TITLE

PYRAZOLOTRIAZINES AS CRF ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to novel compounds, compositions, and methods for the treatment of psychiatric disorders and neurological diseases, including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders, as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress. In particular, the present invention relates to novel pyrazolotriazines, pharmaceutical compositions containing such compounds and their use in treating psychiatric disorders, neurological diseases, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin (POMC) - derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (**1983**); W. Vale et al., *Science* 213:1394 (**1981**)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (**1983**); G.F. Koob, *Persp. Behav. Med.* 2:39 (**1985**); E.B. De

Souza et al., *J. Neurosci.* 5:3189 (**1985**)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (**1989**); J.E. Morley, *Life Sci.* 41:527 (**1987**)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (**1988**)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (**1984**); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (**1987**); R.D. France et al., *Biol. Psychiatry* 28:86 (**1988**); M. Arato et al., *Biol Psychiatry* 25:355 (**1989**)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (**1988**)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (**1984**); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (**1984**); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (**1986**)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (**1989**)]. There is preliminary evidence that tricyclic antidepressants

can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (**1989**)].

It has also been postulated that CRF has a role in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (**1982**); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (**1986**)]. Preliminary studies using the putative CRF receptor antagonist a-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (**1987**), *Brain Research Reviews* 15:71 (**1990**)].

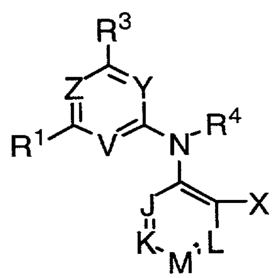
Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (**1985**); K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (**1986**)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)].

It has been further postulated that CRF has a role in immunological, cardiovascular or heart-related diseases such as hypertension, tachycardia and congestive heart failure, stroke, osteoporosis, premature birth, psychosocial dwarfism, stress-induced

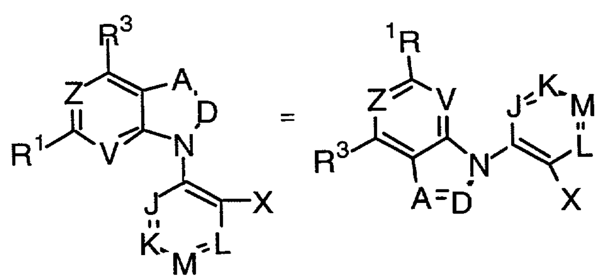
fever, ulcer, diarrhea, post-operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress.

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (a-helical CRF9-41) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

DuPont Merck PCT application US94/11050 describes corticotropin releasing factor antagonist compounds of the formula:

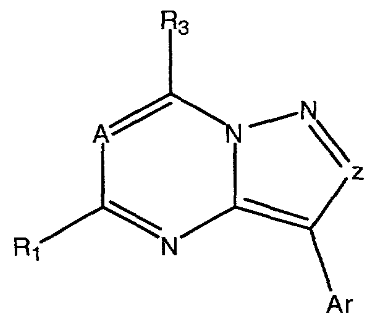


and their use to treat psychiatric disorders and neurological diseases. Included in the description are fused pyridines and pyrimidines of the formula:



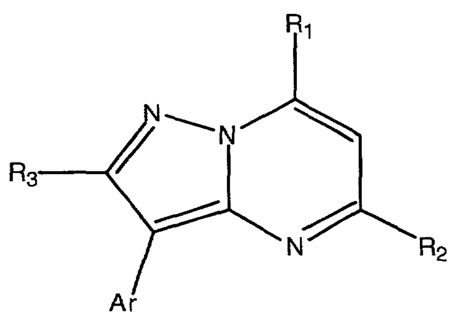
where: V is CR^{1a} or N; Z is CR^{2} or N; A is $CR^{3}0$ or N; and D is CR^{28} or N.

WO 98/03510, published in January, 1998, also describes a series of CRF antagonist compounds having the formula:



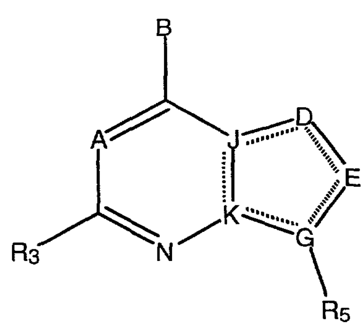
wherein z is N or CR^{2} and A is N or CR.

WO 97/29109, published in August, 1997, similarly describes certain CRF antagonist compounds having the formula:



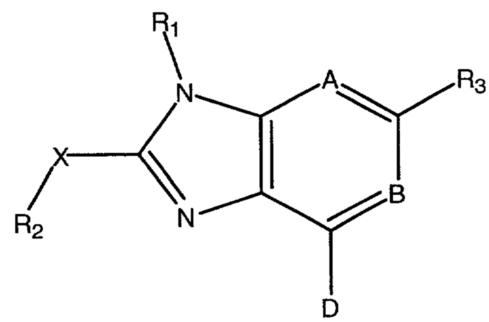
wherein Ar is phenyl, pyridyl and substituted versions thereof.

WO 98/08847, published March 5, 1998, discloses CRF antagonist compounds of the formula:



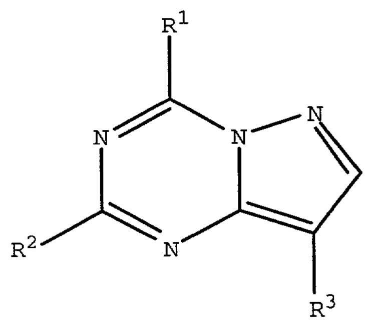
wherein B is selected from a variety of non-aryl groups and R^5 is selected from certain groups such as phenyl or pyridyl or substituted versions thereof.

WO 99/01454, published on January 14, 1999, discloses CRF antagonist compounds of the formula:



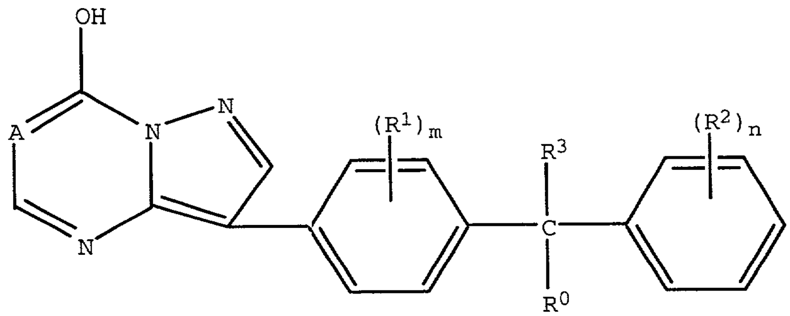
wherein D is an aryl or heteroaryl group and R^1 is selected from certain non-aryl or non-heteroaryl groups.

EP 0 269 859 (Ostuka, 1988) discloses pyrazolotriazine compounds of the formula



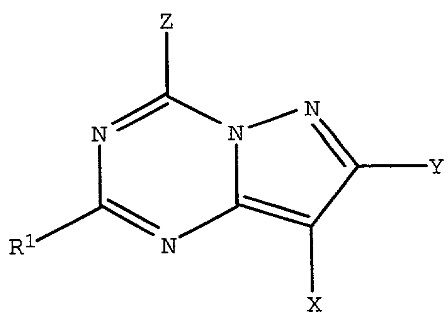
where R^1 is OH or alkanoyl, R^2 is H, OH, or SH, and R^3 is an unsaturated heterocyclic group, naphthyl or substituted phenyl, and states that the compounds have xanthine oxidase inhibitory activity and are useful for treatment of gout.

EP 0 594 149 (Ostuka, 1994) discloses pyrazolotriazine and pyrazolopyrimidine compounds of the formula



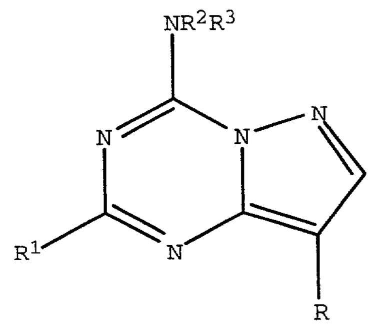
where A is CH or N, R^0 and R^3 are H or alkyl, and R^1 and R^2 are H, alkyl, alkoxyl, alkylthio, nitro, etc., and states that the compounds inhibit androgen and are useful in treatment of benign prostatic hypertrophy and prostatic carcinoma.

US 3,910,907 (ICN Pharma, 1975) discloses pyrazolotriazines of the formula:



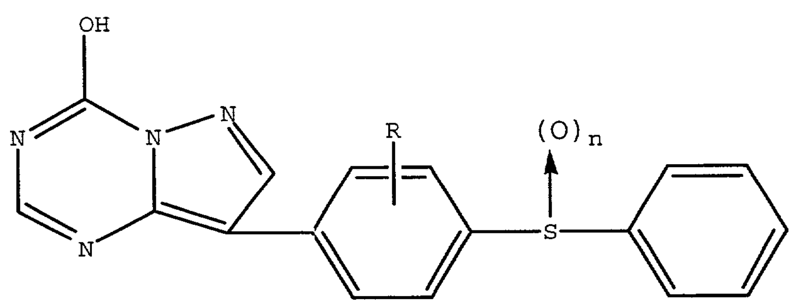
where R1 is CH_3, C_2H_5 or C_6H_5, X is H, C_6H_5, m-$CH_3C_6H_4$, CN, COOEt, Cl, I or Br, Y is H, C_6H_5, o-$CH_3C_6H_4$, or p-$CH_3C_6H_4$, and Z is OH, H, CH_3, C_2H_5, C_6H_5, n-C_3H_7, i-C_3H_7, SH, SCH_3, NHC_4H_9, or $N(C_2H_5)_2$, and states that the compounds are c-AMP phosphodiesterase inhibitors useful as bronchodilators.

US 3,995,039 discloses pyrazolotriazines of the formula:



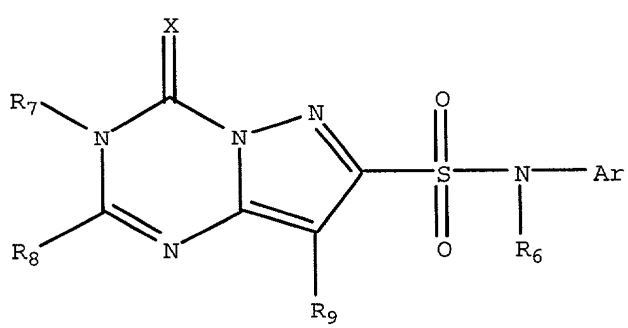
where R^1 is H or alkyl, R^2 is H or alkyl, R^3 is H, alkyl, alkanoyl, carbamoyl, or lower alkylcarbamoyl, and R is pyridyl, pyrimidinyl, or pyrazinyl, and states that the compounds are useful as bronchodilators.

US 5,137,887 discloses pyrazolotriazines of the formula



where R is lower alkoxy, and teaches that the compounds are xanthine oxidase inhibitors and are useful for treatment of gout.

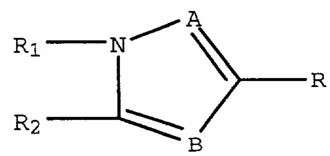
US 4,892,576 discloses pyrazolotriazines of the formula



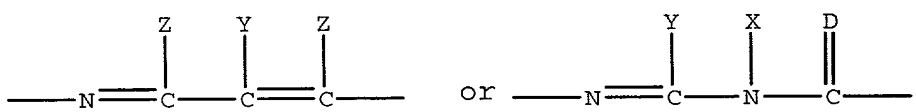
where X is O or S, Ar is a phenyl, naphthyl, pyridyl or thienyl group, R_6-R_8 are H, alkyl, etc., and R_9 is H,

alkyl, phenyl, etc. The patent states that the compounds are useful as herbicides and plant growth regulants.

US 5,484,760 and WO 92/10098 discloses herbicidal compositions containing, among other things, a herbicidal compound of the formula

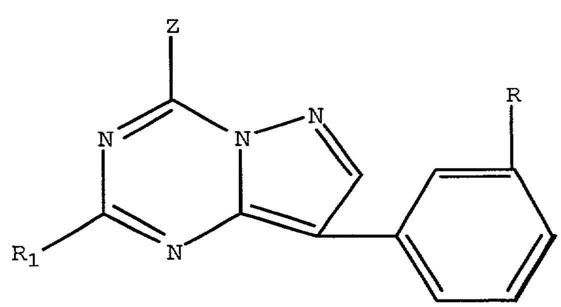


where A can be N, B can be CR_3, R_3 can be phenyl or substituted phenyl, etc., R is $-N(R_4)SO_2R_5$ or $-SO_2N(R_6)R_7$ and R_1 and R_2 can be taken together to form



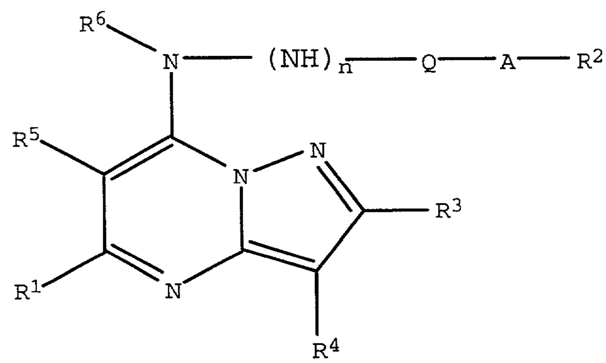
where X, Y and Z are H, alkyl, acyl, etc. and D is O or S.

US 3,910,907 and Senga et al., J. Med. Chem., 1982, 25, 243-249, disclose triazolotriazines cAMP phosphodiesterase inhibitors of the formula



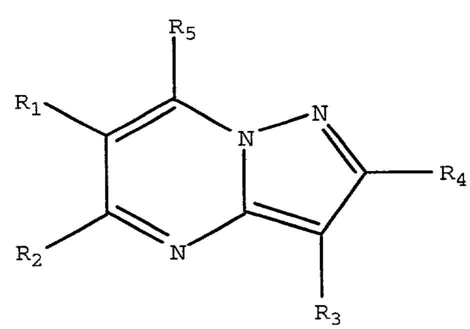
where Z is H, OH, CH_3, C_2H_5, C_6H_5, $n-C_3H_7$, $iso-C_3H_7$, SH, SCH_3, $NH(n-C_4H_9)$, or $N(C_2H_5)_2$, R is H or CH_3, and R_1 is CH_3 or C_2H_5. The reference lists eight therapeutic areas where inhibitors of cAMP phosphodiesterase could have utility: asthma, diabetes mellitus, female fertility control, male infertility, psoriasis, thrombosis, anxiety, and hypertension.

WO95/35298 (Otsuka, 1995) discloses pyrazolopyrimidines and states that they are useful as analgesics. The compounds are represented by the formula



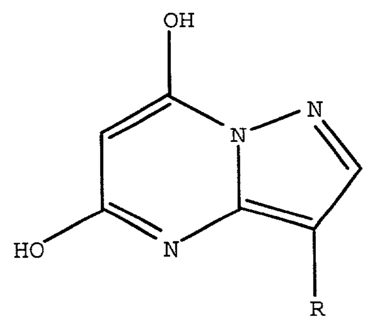
where Q is carbonyl or sulfonyl, n is 0 or 1, A is a single bond, alkylene or alkenylene, R^1 is H, alkyl, etc., R^2 is naphthyl, cycloalkyl, heteroaryl, substituted phenyl or phenoxy, R^3 is H, alkyl or phenyl, R^4 is H, alkyl, alkoxycarbonyl, phenylalkyl, optionally phenylthio-substituted phenyl, or halogen, R^5 and R^6 are H or alkyl.

EP 0 591 528 (Otsuka,1991) discloses anti-inflammatory use of pyrazolopyrimidines represented by the formula



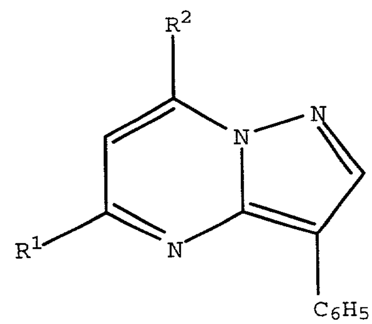
where R_1, R_2, R_3 and R_4 are H, carboxyl, alkoxycarbonyl, optionally substituted alkyl, cycloalkyl, or phenyl, R_5 is SR_6 or NR_7R_8, R_6 is pyridyl or optionally substituted phenyl, and R_7 and R_8 are H or optionally substituted phenyl.

Springer et al, J. Med. Chem., 1976, vol. 19, no. 2, 291-296 and Springer U.S. patents 4021,556 and 3,920,652 disclose pyrazolopyrimidines of the formula



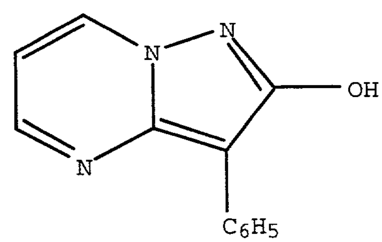
where R can be phenyl, substituted phenyl or pyridyl, and their use to treat gout, based on their ability to inhibit xanthine oxidase.

Joshi et al., J. Prakt. Chemie, 321, 2, 1979, 341-344, discloses compounds of the formula

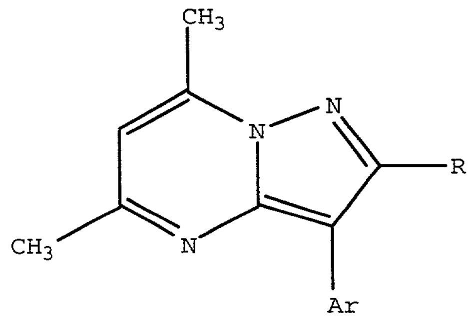


where R^1 is CF_3, C_2F_5, or C_6H_4F, and R^2 is CH_3, C_2H_5, CF_3, or C_6H_4F.

Maquestiau et al., Bull. Soc. Belg., vol.101, no. 2, 1992, pages 131-136 discloses a pyrazolo[1,5-*a*]pyrimidine of the formula

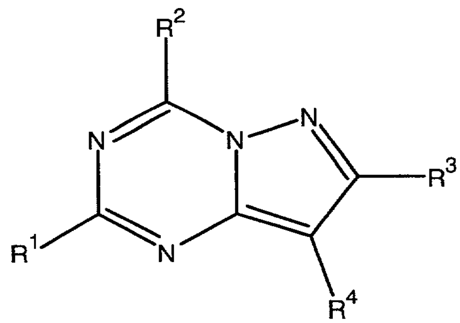


Ibrahim et al., Arch. Pharm. (weinheim) 320, 487-491 (1987) discloses pyrazolo[1,5-*a*]pyrimidines of the formula



where R is NH2 or OH and Ar is 4-phenyl-3-cyano-2-aminopyrid-2-yl.

J. Med. Chem (1982), 25(3), 243-9 discloses compounds of the formula:



wherein R^2 is H, Ph, Pr, Sme, NHEt, NHBu, Net_2, piperidino, OH, NHPr, SH, $OCHMe_2$, Me, Set, Ome or Opr and R^4 is H, Br, C_6H_4Me-3, Ph, CN, CO_2Et or Cl.

Other references which disclose azolopyrimidines inclued EP 0 511 528 (Otsuka, 1992), US 4,997,940 (Dow, 1991), EP 0 374 448 (Nissan, 1990), US 4,621,556 (ICN,1997), EP 0 531 901 (Fujisawa, 1993), US 4,567,263 (BASF, 1986), EP 0 662 477 (Isagro, 1995), DE 4 243 279 (Bayer, 1994), US 5,397,774 (Upjohn, 1995), EP 0 521 622 (Upjohn, 1993), WO 94/109017 (Upjohn, 1994), J. Med. Chem., 24, 610-613 (1981), and J. Het. Chem., 22, 601 (1985) or others as additionally described herein.

SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds which bind to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in mammals.

According to another aspect, the present invention provides novel compounds of formula (I) (described below) which are useful as antagonists of the corticotropin releasing factor and which include pyrazolo[1,5-a][1,3,5]triazines and pyrazolo[1,5-a][1,2,4]triazines. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds of formula (I), and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect, the present invention provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment

of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type;

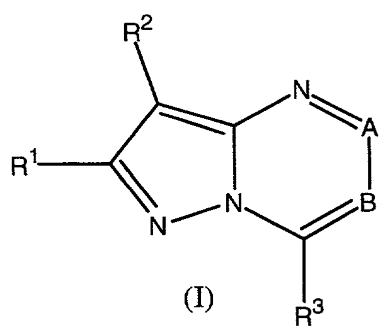
multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in mammals. The preferred uses include treatment of depression and anxiety.

The invention further includes use of a compound of formula I with the variables as recited herein in therapy or the use of a compound of formula I in the manufacture of a medicament for the treatment of CRF related diseases or disorders, including anxiety and depression.

According to a still further aspect of the invention, the compounds provided by this invention (and especially labelled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

DETAILED DESCRIPTION OF INVENTION

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

A equals N or CR^5;

B equals N or CR^4 ;

provided that both A and B cannot be N or provided that A can not be CR^5 and B can not be CR^4 to form a pyrazolopyrimidine; and wherein,

R^1 is independently selected from the group consisting of

H,
halogen,
CN,
C_{1-6} alkyl,
C_{2-10} alkenyl,
C_{2-10} alkynyl,
C_{3-6} cycloalkyl,
C_{1-6} alkyloxy,
C_{1-6} alkylS$(O)_n$,
$-NR^{1a}R^{1B}$ wherein R^{1a} and R^{1b} are independently selected from
H, C_{1-4} alkyl, C_{3-8} cycloalkyl, $-C(O)C_{1-4}$alkyl,
C_{1-6} alkyl$NR^{1a}R^{1b}$,
$NR^{1a}COR^{1b}$,
$-C(O)NR^{1a}R^{1b}$,
$-O-C(O)C_{1-4}$alkyl,

$-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;
X is selected from 0 or $S(O)_n$,

wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy, C_{1-4} haloalkyl, C_{1-4}alkylamino, C_{2-8}dialkylamino, C_{1-4}alkyloxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl or C_{1-4} alkylsulfonyl;

R^2 is selected from the group consisting of H, OR^7, SH, NR^6R^7, $C(OH)R^6R^{6a}$, $C(OR^7)R^6R^{6a}$, $S(O)_nR^{13}$, COR^7, CO_2R^7, $CHR^6(OR^7)R^{6a}$, $OC(O)R^{13}$, NO, NO_2, $NR^6C(O)R^7$, $N(COR^7)_2$, $NR^8CONR^6R^7$ or $NR^6CO_2R^7$; or R^2 is selected from:

C_{1-10} alkyl,
C_{2-10} alkenyl,
C_{2-10} alkynyl,
C_{3-8} cycloalkyl,
C_{3-6} cycloalkyl C_{1-6} alkyl,
C_{1-10} alkyloxy,
C_{1-10} alkyloxyC_{1-10} alkyl,
$-SO_2-C_{1-10}$alkyl
$-SO_2R^{2a}$ wherein R^{2a} is aryl,
$-SO_2R^{2b}$ wherein R^{2b} is heteroaryl,
$-NR^{2C}R^{2D}$ wherein R^{2c} and R^{2d} are independently selected from H, C_{1-8} alkyl, $S(O)_nC_{1-4}$alkyl, $C(O)NR^{2c}R^{2d}$, CO_2C_{1-4}alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxyC_{1-6} alkyl, $-C(O)C_{1-4}$alkyl or R^{2c} and R^{2d} may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,

- halogen,
-CN,
-C(O)-L wherein L is selected from H, $NR^{2c}R^{2d}$, C_{1-6} alkyl or OC_{1-4} alkyl, $O(CH_2)_mOR$ wherein R is C_{1-3} alkyl, $O(CH_2)_m$-$NR^{2c}R^{2d}$,OH, $C(O)OC_{1-6}$alkyl, or aryl or heteroaryl wherein m is 1-4; or

-OC(O)-M wherein M is selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-8} alkoxyalkyl, C_{3-6}cycloalkyl, C_{4-12} cycloalkylalkyl, aryl, C_{1-6} alkylaryl, heteroaryl, C_{1-6} alkylheteroaryl;

n is 0, 1 or 2; and wherein

R^2 is substituted with 0-3 substituents independently selected from R′, R″, R‴ wherein R′, R″ and R‴ are independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkyloxy, hydroxy, or

R^2 is substituted with 0-3 substituents independently selected from:

halogen,

-CN,

$-S(O)_nR^{2e}$ wherein R^{2e} is selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{3-6} cycloalkyl;

$-COR^{2f}$ wherein R^{2f} is selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkylC_{1-4} alkyl;

$-CO_2R^{2f}$,

$-NR^{2g}COR^{2f}$ wherein R^{2g} is selected from H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, wherein R^{2h} is selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkylC_{1-6} alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

C_{3-8} cycloalkyl wherein 0-1 carbon atoms in the C_{4-8} cycloalkyl is replaced by a group selected from -O-, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$, and $-NSO_2R^{2e}$; and wherein N_4 in 1-piperazinyl is substituted with 0-1 substituents selected from R^{2g}, CO_2R^{2e}, COR^{2e} and SO_2R^{2e}; or

the group R^{2i}, R^{2j}, R^{2k}, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, Br, Cl, F, I, C_{1-4} haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl-OR^{2g}, and C_{3-8} cycloalkyl which is substituted with 0-1 R^{21} and in which 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O-, wherein

R^{2i} is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl,. each R^{2i} being substituted with 0-1 OR^{2m} and 0-5 substituents independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I,C_{1-4} haloalkyl, -CN, nitro, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, -$N(COR^{2m})_2$,

$-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2n}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$;

R^{2j} is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl,

thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, OR^{2m}, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted on any nitrogen atom with 0-1 substituents selected from the group R^{2g}, CO_2R^{2e}, COR^{2e} and SO_2R^{2e};

R^{2k} is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for R^{2j}, each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with 0-1 substituents selected from the group R^{2f}, CO_2R^{2e}, COR^{2e} and SO_2R^{2e};

wherein

R^{2l} is H, C_{1-4} alkyl, C_{3-6} cycloalky-C_{1-4} alkyl and C_{3-8} cycloalkyl;

R^{2m} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, C_{1-4} haloalkyl, $R^{2q}S(O)_n$-C_{1-4} alkyl

and $R^{2r}R^{2s}N-C_{2-4}$ alkyl;

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, and C_{1-4} haloalkyl;

R^{2o} and R^{2p} are independently selected at each occurrence from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl and C_{1-4} haloalkyl;

R^{2q} is selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy-C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, aryl, aryl(C_{1-4} alkyl), heteroaryl and heteroaryl (C_{1-4} alkyl)- and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy C_{1-4} haloalkoxy, and dimethylamino;

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N_4 in 1-piperiazinyl is substituted with 0-1 substituents selected from the group R^{2t}, CO_2R^{2q}, COR^{2q} and SO_2R^{2q};

R^{2t} is selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy -C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl - C_{1-6} alkyl, aryl, aryl (C_{1-4} alkyl)-, heteroaryl and heteroaryl (C_{1-4} alkyl);

R^3 is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence

from C_{1-6} alkyl, C_{3-6} cycloalkyl, methylenedioxy, C_{1-4} alkyloxy-C_{1-4} alkyloxy, $-OR^{2m}$, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, $-NO_2$, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, -$NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$;

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, F, I, C_{1-4} haloalkyl, -CN, $NR^{2g}R^{2h}$, nitro, -OR^{2m}, -SH, $-S(O)_nR^{2n}$, COR^{2m}, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, -$N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group R^{2g}, CO_2R^{3a}, COR^{3a} and SO_2R^{3a} wherein,

R^{3a} is selected from the group C_{1-6} alkyl, C_{1-4} cycloalkyl-C_{1-6} alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and dimethylamino;

R^4 and R^5 are independently selected at each occurrence from H, Br, Cl, F, I, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-4} alkylamino,

(C_{1-4} alkyl)$_2$ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of C_{1-7} alkyl, C_{3-8} cycloalkyl, Br, Cl, F, I, -C(O)H, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-6} alkylamino and (C_{1-4} alkyl)$_2$ amino and wherein R^4 and R^5 non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, -OC_{1-6}-alkyl and C_{1-6} haloalkyl, C_{1-6} alkyl, C_{3-7} c-alkyl, C_{1-6} alkyl$(OH)_nCO_2R$ wherein R is H or C_{1-6} alkyl, C_{1-6} alkyl$(OH)_n$,wherein n is 0-3 or R^4 and R^5 may join together to form a C_{3-6} alkylene chain;

R^6, R^{6a} and R^7 are independently selected from: H, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{1-10} haloalkyl, C_{2-8} alkoxyalkyl, C_{4-12} cycloalkylalkyl, C_{5-10} cycloalkenyl, C_{6-14} cycloalkenylalkyl;

R^6, R^{6a} and R^7 are substituted with 0-6 substituents independently selected from halogen, C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy, C_{1-4} haloalkyl;

with the proviso that the compounds of Formula I with R^1, R^2, R^3, R^4 and R^5 as specifically defined below are excluded:

(a) a compound of formula I wherein A = CR^5 with R^5 o-hydroxyphenyl, B = N, R^3 = o-hydroxyphenyl, R^1=SMe and R^2 =CN (Registry Reference 23/IS98062) and

(b) a compound of formula I wherein A=CR^5, R^5=CH_3, B = N, R^1 = Ph, R^2 = Br and R^3 is Ph;

(c) a compound of formula I wherein A= CR^5, R^5 =p-Cl-phenyl, B= N, R^1 = Me, R^2 = H and R^3 = p-CF_3-phenyl(Registry reference 152/IS98062);

(d) a compound of formula I wherein A= CR^5, R^5 = phenyl, B= N, R^1 = Me, R^2 = H and R^3 = p-CF_3-phenyl(Registry reference 153/IS98062);

(e) a compound of formula I wherein A= CR^5, R^5 = ethyl, B= N, R^1 = Me, R^2 = H and R^3 = N-methyl-piperiazin-N-yl (registry reference 184/IS98062);

(f) a compound of formula I wherein A=CR^5, R^5 is p-Cl-Ph, R^1=H, R^2=H and R^3 = p-CF_3-Ph (Registry reference 9/IS98179);

(g) a compound of formula I wherein A=CR^5, R^5=p-Cl-Ph, R^1= CH_3, R^2=H, R^3= p-CF_3-Ph (Registry reference 10/IS98179);

(h) a compound of formula I wherein A=CR^5, R^5=Ph, R^1 = Me, R^2=H, R^3=p-CF_3-Ph (Registry reference 11/IS98179);

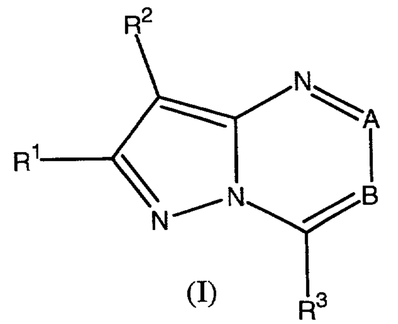
(i) a compound of formula I wherein A=CR^5, R^5=Ph, R^1=H, R^2=H, R^3=p-CF_3-Ph (Registry reference 12/IS98179);

(j) a compound of formula I wherein A=CR^5, R^3 = Ph and R^2 is H, Br, CN, CO_2Et or Cl (J. Med. Chem. (1982), 25(3), 243-9;

(k) a compound of formula I wherein A=CR^5, R^5 = CH_3, C_2H_5 or Ph, R^1=H, R^2=H and R^3=Ph (US 3,910,907).

[1'] The present invention preferrably relates to

a novel compound of formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt thereof, wherein:

A equals N or CR^5;

B equals N or CR^4 ;

provided that both A and B cannot be N or provided that A can not be CR^5 and B can not be CR^4 to form a pyrazolopyrimidine; and wherein,

R^1 is independently selected from the group consisting of

H,
halogen,
CN,
C_{1-6} alkyl,
C_{2-10} alkenyl,
C_{2-10} alkynyl,
C_{3-6} cycloalkyl,
C_{1-6} alkyloxy,
C_{1-6} alkylS(O)$_n$,
$-NR^{1a}R^{1B}$ wherein R^{1a} and R^{1b} are independently selected from

H, C_{1-4} alkyl, C_{3-8} cycloalkyl, $-C(O)C_{1-4}$alkyl,
C_{1-6} alkyl$NR^{1a}R^{1b}$,
$NR^{1a}COR^{1b}$,
$-C(O)NR^{1a}R^{1b}$,
$-O-C(O)C_{1-4}$alkyl,

$-XR^{1c}$ wherein R^{1c} is selected from H or $-C_{1-4}$ alkylaryl;
X is selected from O or $S(O)_n$,

wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy, C_{1-4} haloalkyl, C_{1-4}alkylamino, C_{2-8}dialkylamino, C_{1-4}alkyloxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl or C_{1-4} alkylsulfonyl;

R^2 is selected from the group consisting of OR^7, SH, NR^6R^7, $C(OH)R^6R^{6a}$, $C(OR^7)R^6R^{6a}$, $S(O)_nR^{13}$, COR^7, CO_2R^7, $CHR^6(OR^7)R^{6a}$, $OC(O)R^{13}$, NO, NO_2, $NR^6C(O)R^7$, $N(COR^7)_2$, $NR^8CONR^6R^7$ or $NR^6CO_2R^7$; or R^2 is selected from:

C_{1-10} alkyl,
C_{2-10} alkenyl,
C_{2-10} alkynyl,
C_{3-8} cycloalkyl,
C_{3-6} cycloalkyl C_{1-6} alkyl,
C_{1-10} alkyloxy,
C_{1-10} alkyloxyC_{1-10} alkyl,
$-SO_2-C_{1-10}$alkyl
$-SO_2R^{2a}$ wherein R^{2a} is aryl,
$-SO_2R^{2b}$ wherein R^{2b} is heteroaryl,
$-NR^{2c}R^{2D}$ wherein R^{2c} and R^{2d} are independently selected from
H, C_{1-8} alkyl, $S(O)_nC_{1-4}$alkyl, $C(O)NR^{2c}R^{2d}$, CO_2C_{1-4}alkyl,
C_{3-8} cycloalkyl, C_{1-6} alkyloxyC_{1-6} alkyl, $-C(O)C_{1-4}$alkyl

or R^{2c} and R^{2d} may join to form a heterocyclic ring having 0-3 heteroatoms selected from O, N or S,

-C(O)-L wherein L is selected from H, $NR^{2c}R^{2d}$, C_{1-6} alkyl $O(CH_2)_mOR$ wherein R is C_{1-3} alkyl, $O(CH_2)_m$- $NR^{2c}R^{2d}$,OH, $C(O)OC_{1-6}$alkyl, or aryl or heteroaryl wherein m is 1-4; or

-OC(O)-M wherein M is selected from C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-8} alkoxyalkyl, C_{3-6}cycloalkyl, C_{4-12} cycloalkylalkyl, aryl, C_{1-6} alkylaryl, heteroaryl, C_{1-6} alkylheteroaryl;

n is 0, 1 or 2; and wherein

R^2 is substituted with 0-3 substituents independently selected from R′, R″, R″′ wherein R′, R″ and R″′ are independently selected from C_{1-6} alkyl, C_{3-7} cycloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkyloxy, hydroxy, or

R^2 is substituted with 0-3 substituents independently selected from:

halogen,

-CN,

$-S(O)_nR^{2e}$ wherein R^{2e} is selected from C_{1-4} alkyl, C_{1-4} haloalkyl,C_{1-4} alkyloxy C_{1-4} alkyl, C_{3-6} cycloalkyl;

$-COR^{2f}$ wherein R^{2f} is selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkylC_{1-4} alkyl;

$-CO_2R^{2f}$,

$-NR^{2g}COR^{2f}$ wherein R^{2g} is selected from H, C_{1-6} alkyl, C_{3-7} cycloalkyl,C_{3-6} cycloalkyl C_{1-6} alkyl;

$-N(COR^{2f})_2$,

$-NR^{2g}CONR^{2f}R^{2h}$, wherein R^{2h} is selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy C_{1-4} alkyl, C_{3-6} cycloalkyl and C_{3-6} cycloalkylC_{1-6} alkyl;

$-NR^{2g}CO_2R^{2e}$,

$-CONR^{2g}R^{2h}$,

1-morpholinyl,

1-piperidinyl,

1-piperazinyl,

and

C_{3-8} cycloalkyl wherein 0-1 carbon atoms in the C_{4-8} cycloalkyl is replaced by a group selected from $-O-$, $-S(O)_n-$, $-NR^{2g}-$, $-NCO_2R^{2e}$, $-NCOR^{2e}$, and $-NSO_2R^{2e}$; and wherein N_4 in 1-piperazinyl is substituted with 0-1 substituents selected from R^{2g}, CO_2R^{2e}, COR^{2e} and SO_2R^{2e}; or

the group R^{2i}, R^{2j}, R^{2k}, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, Br, Cl, F, I, C_{1-4} haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkyl-OR^{2g}, and C_{3-8} cycloalkyl which is substituted with 0-1 R^{2l} and in which 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O-, wherein

R^{2i} is selected from aryl wherein aryl includes phenyl, naphthyl, indanyl and indenyl, each R^{2i} being substituted with 0-1 OR^{2m} and 0-5

substituents independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2n}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$;

R^{2j} is selected from heteroaryl wherein heteroaryl includes pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-s-oxide, 2,3-dihydro-benzothienyl-S-dioxide, indolinyl, benzoxazolin-2-onyl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, OR^{2m}, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heteroaryl being substituted on any nitrogen atom with 0-1 substituents selected from the group R^{2g}, CO_2R^{2e}, COR^{2e} and SO_2R^{2e};

R^{2k} is heterocyclyl which is a saturated or partially saturated heteroaryl as defined for R^{2j}, each heterocyclyl being substituted on 0-4 carbon atoms with a substituent independently selected from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2h}$, $-COR^{2m}$, $-OC(O)R^{2h}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $-CONR^{2o}R^{2p}$ and each heterocyclyl being substituted on any nitrogen atom with

0-1 substituents selected from the group R^{2f}, CO_2R^{2e}, COR^{2e} and SO_2R^{2e};

wherein

R^{21} is H, C_{1-4} alkyl, C_{3-6} cycloalky-C_{1-4} alkyl and C_{3-8} cycloalkyl;

R^{2m} is H, C_{1-6} alkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, C_{1-4} haloalkyl, $R^{2q}S(0)_n$-C_{1-4} alkyl and $R^{2r}R^{2s}N$-C_{2-4} alkyl;

R^{2n} is H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl-C_{1-6} alkyl, C_{1-2} alkyloxy C_{1-2} alkyl, and C_{1-4} haloalkyl;

R^{2o} and R^{2p} are independently selected at each occurrence from H, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl and C_{1-4} haloalkyl;

R^{2q} is selected from C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy-C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl- C_{1-6} alkyl, aryl, aryl(C_{1-4} alkyl), heteroaryl and heteroaryl (C_{1-4} alkyl)- and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy C_{1-4} haloalkoxy, and dimethylamino;

$R^{2r}R^{2s}$ taken together with the N form 1-pyrrolidinyl, 1-morpholinyl, 1-piperidinyl or 1-piperazinyl wherein N_4 in 1-piperiazinyl is substituted with 0-1 substituents selected from the group R^{2t}, CO_2R^{2q}, COR^{2q} and SO_2R^{2q};

R^{2t} is selected from H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy -C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl - C_{1-6} alkyl, aryl, aryl (C_{1-4} alkyl)-, heteroaryl and heteroaryl (C_{1-4} alkyl);

R^3 is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom;

aryl is selected from phenyl, naphthyl, indanyl and indenyl, each aryl being substituted with 0-5 substituents independently selected at each occurrence from C_{1-6} alkyl, C_{3-6} cycloalkyl, methylenedioxy, C_{1-4} alkyloxy-C_{1-4} alkyloxy, -OR^{2m}, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, -NO_2, -SH, -$S(O)_nR^{2n}$, -COR^{2m}, -CO_2R^{2m}, -$OC(O)R^{2n}$, -$NR^{2g}COR^{2m}$, -$N(COR^{2m})_2$, -$NR^{2g}CONR^{2o}R^{2p}$, -$NR^{2g}CO_2R^{2h}$, -$NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$;

heteroaryl is selected from the group pyridyl, pyrimidyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzoxazolyl, isoxazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzo-furanyl, 2,3-dihydrobenzothienyl, 2,3-dihydro-benzothienyl-S-oxide, 2,3-dihydrobenzothienyl-s-dioxide, indolinyl, benzoxazolin-2-on-yl, benzodioxolanyl and benzodioxane, each heteroaryl being substituted at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, F, I, C_{1-4} haloalkyl, -CN, $NR^{2g}R^{2h}$, nitro, -OR^{2m}, -SH, -$S(O)_nR^{2n}$, COR^{2m}, -CO_2R^{2m}, -$OC(O)R^{2n}$, -$NR^{2g}COR^{2m}$, -$N(COR^{2m})_2$, -$NR^{2g}CONR^{2o}R^{2p}$ and each heteroaryl being substituted at any nitrogen atom with 0-1 substituents selected from the group R^{2g}, CO_2R^{3a}, COR^{3a} and SO_2R^{3a} wherein,

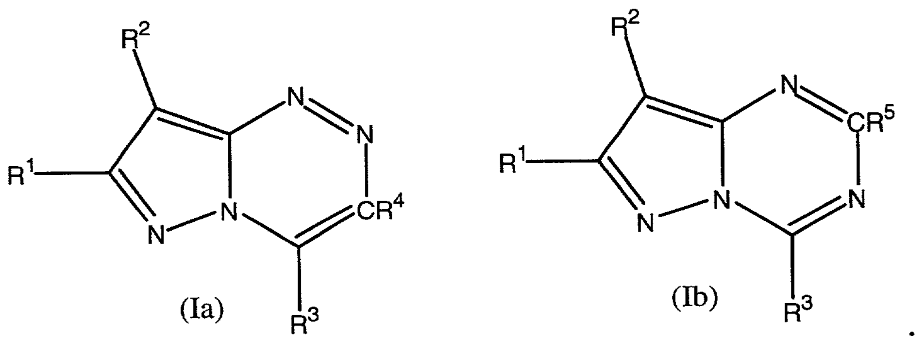
R^{3a} is selected from the group C_{1-6} alkyl, C_{1-4} cycloalkyl-C_{1-6} alkyl and benzyl, each benzyl being substituted on the aryl moiety with 0-1 substituents selected from the group C_{1-4} alkyl, Br, Cl, F, I, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and dimethylamino;

R^4 and R^5 are independently selected at each occurrence from H, Br, Cl, F, I, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, amino, C_{1-4} alkylamino, $(C_{1-4}$ alkyl$)_2$ amino and phenyl, each phenyl is substituted with 0-3 groups selected from the group consisting of C_{1-7} alkyl, C_{3-8} cycloalkyl, Br, Cl, F, I, -C(O)H, C_{1-4} haloalkyl, nitro, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-6} alkylamino and $(C_{1-4}$ alkyl$)_2$ amino and wherein R^4 and R^5 non-phenyl groups may be substituted with 0-5 substituents selected from OH, halogen, -C(O)H, -OC_{1-6}-alkyl and C_{1-6} haloalkyl, C_{1-6} alkyl, C_{3-7} c-alkyl, C_{1-6} alkyl$(OH)_nCO_2R$ wherein R is H or C_{1-6} alkyl, C_{1-6} alkyl$(OH)_n$,wherein n is 0-3 or R^4 and R^5 may join together to form a C_{3-6} alkylene chain;

R^6, R^{6a} and R^7 are independently selected from: H, C_{1-10} alkyl, C_{3-10} cycloalkyl, C_{3-10} alkenyl, C_{3-10} alkynyl, C_{1-10} haloalkyl, C_{2-8} alkoxyalkyl, C_{4-12} cycloalkylalkyl, C_{5-10} cycloalkenyl, C_{6-14} cycloalkenylalkyl;

R^6, R^{6a} and R^7 are substituted with 0-6 substituents independently selected from halogen, C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-6} alkyloxy, C_{1-4} haloalkyl.

[2] The present invention also relates to compounds of formula (Ia) and (Ib) below with the variables as recited above in group [1] or [1']:



[3] The present invention relates to a compound as described directly above in [1], [1'] or [2] wherein

R^1 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, $-XR^{1c}$ wherein R^1 is substituted with 0-6 substituents selected from halogen, C_{1-4} alkyl or C_{1-4} haloalkyl;

R^2 is selected from C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-8} cycloalkyl, C_{3-6} cycloalkyl C_{1-6} alkyl, $-NR^{2c}R^{2d}$ wherein R^2 is unsubstituted or substituted with 1-3 substitutents independently selected from the group R^{2i}, R^{2j}, R^{2k}, C_{1-6} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, Br, Cl, F, I, C_{1-4} haloalkyl, $-OR^{2g}$, $-NR^{2g}R^{2h}$, $-C_{1-6}$ alkylOR^{2g}, and C_{3-8} cycloalkyl which is substituted with 0-1 R^{21} and in which 0-1 carbons of C_{4-8} cycloalkyl is replaced by -O-.

[4] The present invention also relates to a compound described directly above in group [1] or [1'], [2] or [3] wherein R^3 is selected from an aryl group selected from

phenyl or substituted versions thereof or a heteroaryl group selected from pyridyl or substituted versions thereof.

[5] The present invention relates to a compound described directly above in [1], [1′], [2], [3], or [4] wherein R^3 is substituted with 0-4 substituents independently selected from halogen, C_{1-4} alkyloxy, C_{1-6} alkyl or NR′R″ wherein R′ and R″ are independently selected from H or C_{1-6} alkyl.

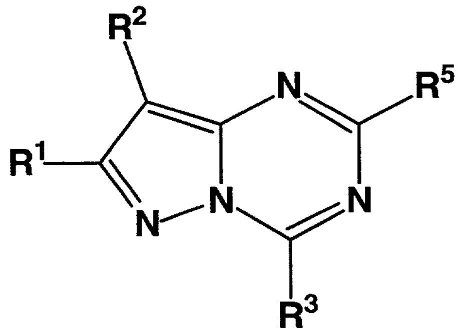
[6] The present invention preferrably relates to a compound as described directly above in groups [1], [1′], [2], [3], [4] or [5] wherein R^3 is selected from 2,4-dichlorophenyl, 2-chloro-4-methoxyphenyl, 2,4,6-trimethylphenyl, 2,4,6-trimethoxyphenyl, 2-dimethylamino-4-methyl-pyridin-5-yl, 2,4-dichloro-5-fluorophenyl, 2-chloro-4-methoxy-5-fluorophenyl, 2-methyl-4-methoxyphenyl, 2-methyl-4,6-dimethoxyphenyl, 2-chloro-4,5-dimethoxyphenyl or 2-chloro-4,6-dimethoxyphenyl.

[7] The present invention also preferrably relates to a compound as described in the group [1], [1′], [2], [3], [4], [5], or [6] wherein R^2 is selected from C_1 alkyl of the formula -CR′R″R″′ wherein R′, R″ and R″′ are independently selected from H, C_{1-6} alkyl, C_{3-7} cycloalkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkyloxyC_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy, with the proviso that each of R′,R″ and R′″ cannot be H;

or R^2 is selected from $NR^{2c}R^{2d}$ wherein R^{2c} and R^{2d} are independently selected from H or C_{1-6} alkyl.

[8] The present invention preferrably relates to a compound according to groups [1]-[7] and [1'] wherein R^3 is selected from an aryl or heteroaryl group attached through an unsaturated carbon atom wherein, aryl is phenyl, each phenyl being substituted with 0-5 substituents independently selected at each occurrence from C_{1-6} alkyl, C_{3-6} cycloalkyl, methylenedioxy, C_{1-4} alkyloxy-C_{1-4} alkyloxy, $-OR^{2m}$, Br, Cl, F, I, C_{1-4} haloalkyl, -CN, $-NO_2$, -SH, $-S(O)_nR^{2n}$, $-COR^{2m}$, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$, $-NR^{2g}CO_2R^{2h}$, $-NR^{2o}R^{2p}$ and $CONR^{2o}R^{2p}$ and up to 1 phenyl, each phenyl substituent being substituted with 0-4 substituents selected from the group C_{1-3} alkyl, C_{1-3} alkoxy, Br, Cl, F, I, -CN, dimethylamino, CF_3, C_2F_5, OCF_3, SO_2Me and acetyl and wherein, heteroaryl is selected at each occurrence from pyridyl, each pyridyl being substitued at 0-4 carbon atoms with a substituent independently selected at each occurrence from the group C_{1-6} alkyl, C_{3-6} cycloalkyl, Br, F, I, C_{1-4} haloalkyl, -CN, nitro, $-OR^{2m}$, -SH, $-S(O)_nR^{2n}$, COR^{2m}, $-CO_2R^{2m}$, $-OC(O)R^{2n}$, $-NR^{2g}COR^{2m}$, $-N(COR^{2m})_2$, $-NR^{2g}CONR^{2o}R^{2p}$ and each pyridyl being substituted at any carbon atom with 0-1 substituents selected from the group R^{2g}, CO_2R^{3a}, COR^{3a} and SO_2R^{3a} .

[9] The present invention preferrably relates to a compound of formula (Ia)



(Ia)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is independently selected at each occurrence from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, halo, CN, C_1-C_4 haloalkyl, C_1-C_{12} hydroxyalkyl, C_2-C_{12} alkoxyalkyl, C_2-C_{10} cyanoalkyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, NR^9R^{10}, C_1-C_4 alkyl-NR^9R^{10}, NR^9COR^{10}, OR^{11}, SH or $S(O)_nR^{12}$;

R^2 is selected from:

-H, OR^7, SH, $S(O)_nR^{13}$, COR^7, CO_2R^7, $CHR^6(OR^7)R^{6a}$, $OC(O)R^{13}$, $CH(OH)R^6$, $C(OH)R^6R^{6a}$, $C(OR^7)R^6R^{6a}$, NO, NO_2, NR^6COR^7, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^6CO_2R^7$, NR^6R^7, $NR^6S(O)_2R^7$, $N(S(O)_2R^7)_2$, $N(OR^7)R^6$ or $CONR^6R^7$;

or

-C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12} cycloalkylalkyl or C_6-C_{10} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;

R^3 is selected from phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indanyl, 1,2-benzopyranyl, 3,4-dihydro-1,2-benzopyranyl, tetralinyl, each R^3 optionally substituted with 1 to 5 substituents, each Ar is attached via an unsaturated carbon atom, wherein the substitutents are independently selected at each occurrence from: C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, NO_2, halo, CN, C_1-C_4 haloalkyl, NR^6R^7, NR^8COR^7, $NR^8CO_2R^7$, COR^7, OR^7, $CONR^6R^7$, $CO(NOR^9)R^7$, CO_2R^7, or $S(O)_nR^7$, where each such C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_4 alkyl, NO_2, halo, CN, NR^6R^7, NR^6COR^7, $NR^7CO_2R^7$, COR^7 OR^7, $CONR^6R^7$, CO_2R^7, $CO(NOR^9)R^7$, or $S(O)_nR^7$;

R^5 is selected from H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl; halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl and heterocyclyl;
or
halo, CN, $-NR^6R^7$, NR^9COR^{10}, $-NR^6S(O)_nR^7$, $S(O)_nNR^6R^7$, C_1-C_4 haloalkyl, $-OR^7$, SH or $-S(O)_nR^{12}$;

R^6, R^{6a} and R^7 are independently selected at each occurrence from:

-H,

$-C_1-C_{10}$ alkyl, C_3-C_{10} alkenyl, C_3-C_{10} alkynyl, C_1-C_{10} haloalkyl with 1-10 halogens, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_5-C_{10} cycloalkenyl, or C_6-C_{14} cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$, aryl, heteroaryl or heterocyclyl,

-aryl, aryl(C_1-C_4 alkyl), heteroaryl, heteroaryl(C_1-C_4 alkyl), heterocyclyl or heterocyclyl(C_1-C_4 alkyl);

alternatively, NR^6R^7 and $NR^{6a}R^{7a}$ are independently piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine, each optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^8 is independently selected at each occurrence from H or C_1-C_4 alkyl;

R^9 and R^{10} are independently selected at each occurrence from H, C_1-C_4 alkyl, or C_3-C_6 cycloalkyl;

R^{11} is selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_3-C_6 cycloalkyl;

R^{12} is C_1-C_4 alkyl or C_1-C_4 haloalkyl;

R^{13} is selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_2-C_8 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-

C_{12} cycloalkylalkyl, aryl, aryl(C_1-C_4 alkyl)-, heteroaryl or heteroaryl(C_1-C_4 alkyl)-;

R^{15} and R^{16} are independently selected at each occurrence from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_4-C_{16} cycloalkylalkyl, except that for $S(O)_nR^{15}$, R^{15} cannot be H;

aryl is phenyl or naphthyl, each optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, pyranyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, pyrazolyl, 2,3-dihydrobenzothienyl or 2,3-dihydrobenzofuranyl, each being optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, $-COR^{15}$, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{16}R^{15}$, and $CONR^{16}R^{15}$;

heterocyclyl is saturated or partially saturated heteroaryl, optionally substituted with 1 to 5 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{15}$, COR^{15}, CO_2R^{15}, $OC(O)R^{15}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{15}$, $NR^{15}R^{16}$, and $CONR^{16}R^{15}$;

n is independently at each occurrence 0, 1 or 2.

[10] The present invention also relates to a compound according to groups [1′] and [1]-[9] wherein R^3 is substituted with 2-4 substituents.

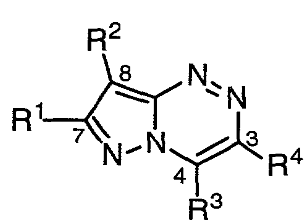
[11] The present invention also relates to a compound according to groups [1′] and [1]-[10] wherein R^2 is substituted with 1-4 substituents.

[12] The present invention also relates to a compound according to groups [1′] and [1]-[9] wherein R^2 is selected from 3-pentyl, NEt_2, butyl, $NHCH(CH_2OMe)_2$, $NHCH(CH_2OEt)_2$, $NHCH(Et)CH_2OMe$, NH-3-heptyl, NH-3-pentyl, NH-2-butyl, NH-3-hexyl, $NHCH(CH_2Ph)CH_2OMe$, $NHCH(Et)CH_2CH_2OMe$, NH-cyclobutyl, NH-cyclopentyl, NEtPr, NEtBu, NMePr, NMePh, Npr_2, $NPr(CH_2\text{-c-}C_3H_5)$, $N(CH_2CH_2OMe)_2$, morpholino, $N(CH_2Ph)CH_2CH_2OMe$, $N(Me)CH_2CH_2OMe$, $N(Et)CH_2CH_2OMe$, $N(CH_2\text{-c-}C_3H_5)CH_2CH_2OMe$, $N(CH_2\text{-c-}C_3H_5)Pr$, $N(CH_2\text{-c-}C_3H_5)Et$, OEt, $OCH(Et)CH_2OMe$, $OCH(Et)CH_2CH_2OMe$, $OCH(Me)CH_2CH_2OMe$, O-3-pentyl, O-2-pentyl, S-3-pentyl, S-2-pentyl, SEt, S(O)Et, SO_2Et, S-3-pentyl, S(O)-3-pentyl, SO_2-3-pentyl, S-2-pentyl, S(O)-2-pentyl, SO_2-2-pentyl, $CH(CO_2Et)_2$, $C(Et)(CO_2Et)_2$, $CH(Et)CH_2OH$, $CH(Et)CH_2OMe$, $CH(Et)CH_2CH_2OMe$, $CONMe_2$, $COCH_3$, COEt, COPr, CO-2-pentyl, CO-3-pentyl, $CH(OH)CH_3$, $C(OH)Me_2$, C(OH)Ph-3-pyridyl, $CH(OMe)CH_3$, CH(OMe)Et, CH(OMe)Pr, $CH(OEt)CH_3$, $CH(OPr)CH_3$, 2-pentyl, 2-butyl, cyclobutyl, cyclopentyl, CH(Me)cyclobutyl, CH(OMe)cyclobutyl, CH(OH)cyclobutyl, CH(Me)cyclopropyl, CH(OMe)cyclopropyl, CH(OH)cyclopropyl, CH(Et)cyclobutyl, CH(Et)cyclopropyl, CH(OMe)cyclobutyl, CH(OMe)cyclopropyl,

CH(OEt)cyclobutyl, CH(OEt)cyclopropyl, CH(Me)CH$_2$-cyclobutyl, CH(OMe)CH$_2$-cyclobutyl, CH(OH)CH$_2$-cyclobutyl, CH(Me)CH$_2$-cyclopropyl, CH(OMe)CH$_2$-cyclopropyl, CH(OH)CH$_2$-cyclopropyl, CH(Et)CH$_2$-cyclobutyl, CH(Et)CH$_2$-cyclopropyl, CH(OMe)CH$_2$-cyclobutyl, CH(OMe)CH$_2$-cyclopropyl, CH(OEt)CH$_2$-cyclobutyl, CH(OEt)CH$_2$-cyclopropyl, CH(CH$_2$OMe)cyclobutyl, CH(CH$_2$OMe)cyclopropyl, CH(CH$_2$OEt)cyclobutyl, CH(CH$_2$OEt)cyclopropyl, CH(cyclobutyl)$_2$, CH(cyclopropyl)$_2$, CH(Et)CH$_2$CONMe$_2$, CH(Et)CH$_2$CH$_2$NMe$_2$, CH(CH$_2$OMe)Me, CH(CH$_2$OMe)Et, CH(CH$_2$OMe)Pr, CH(CH$_2$OEt)Me, CH(CH$_2$OEt)Et, CH(CH$_2$OEt)Pr, CH(CH$_2$C$\equiv$CMe)Et, CH(CH$_2$C$\equiv$CMe)Et.

[13] The present invention further relates to a compound of formula I or Ia according to groups [1'] and [1]-[12] above wherein R^3 is selected from 2,4-Cl$_2$-Ph, 2,4,6-Me$_3$-Ph, 2,4-Me$_2$-Ph, 2-Me-4-MeO-Ph, 2-Cl-4-MeO-Ph, 2-Cl-4,5-(MeO)$_2$-Ph, 2-Cl-4-MeO-5-F-Ph, 2-Me-4-MeO-5-F-Ph, 2,5-(Me)$_2$-4-MeO-Ph, 2-Me-4-NMe$_2$-Ph, 2-CF$_3$-4-MeO-Ph, 2-Me-4-(COMe)-Ph, 2-Me-6-Me$_2$N-pyrid-3-yl, 4-Me-2-Me$_2$N-pyrid-5-yl, 2-Me-6-MeO-pyrid-3-yl, 4-Me-2-MeO-pyrid-5-yl.

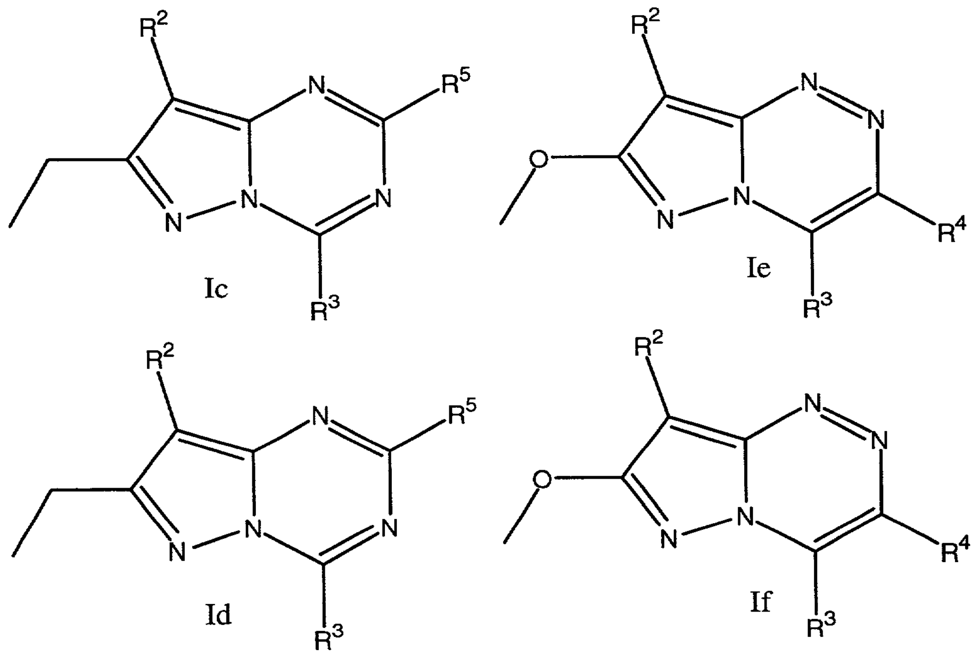
[14] The present invention also relates to a compound of formula Ib



having R^1-R^4 as defined in groups [1]-[13] above.

[15] In a preferred embodiment, the present invention relates to a compound according to group [14] wherein R^1 is selected from H, CH_3, C_2H_5, OCH_3; R4 is selected from H, OCH_3, CH_3 and C_2H_5; R^2 is selected from $CH(C_2H_5)_2$, $CH(c\text{-}C_3H_5)_2$, $CHC_2H_5(c\text{-}C_3H_5)$, $CH(C_2H_5)_2$, $CH(c\text{-}C_3H_5)_2$; and R^3 is selected from 2,4-Cl_2-Ph, 2-Cl-4-CH_3O-Ph, 2,4,6-$(CH_3)_3$-Ph, 2-Cl-4-CF_3-Ph and 2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl.

[16] The present invention also relates to compounds of formula Ic, Id, Ie and If



and the pharmaceutically acceptable salts thereof wherein R^2, R^3, R^4 and R^5 are as defined in groups [1]-[15] above.

[17] The present invention also relates to a method of antagonizing a CRF-1 receptor in mammals including humans wherein binding to the receptor causes and ultimately results in the treatment of affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune

suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of Formula I, Ia, Ib, Ic, Id, Ie or If according to groups [1]-[16] and [1′] above with the proviso that, in the case of compounds of group [1], provisos (a) and (b) are not present.

[18] The present invention also relates to use of a compound according to groups [1]-[16] and [1′] in therapy.

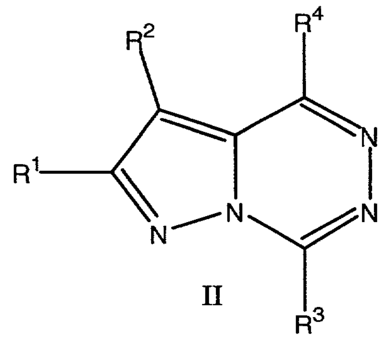
[19] The present invention also provides pharmaceutical compositions comprising compounds of Formula I, Ia, Ib, Ic, Id, Ie, or If with the variables as recited above in groups [1]-[16] and [1′] and a pharmaceutically acceptable carrier.

[20] The present invention also relates to compounds according to group [9] wherein R^2 is NR^6R^7, OR^7 or

-C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_4-C_{12} cycloalkylalkyl or C_6-C_{10}

cycloalkenylalkyl, each optionally substituted with 1 to 3 substituents independently selected at each occurrence from C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, C_1-C_4 haloalkyl, cyano, OR^{15}, SH, $S(O)_nR^{13}$, COR^{15}, CO_2R^{15}, $OC(O)R^{13}$, NR^8COR^{15}, $N(COR^{15})_2$, $NR^8CONR^{16}R^{15}$, $NR^8CO_2R^{13}$, $NR^{16}R^{15}$, $CONR^{16}R^{15}$.

[21] The present invention also relates to a compound of formula II



II

or a pharmaceutically acceptable salt or isomer thereof wherein R^1-R^4 and the other variables are as defined in groups [1'] and [1]-[20].

[22] The invention further relates to pharmaceutical compositions comprising the compound of group [21] and a pharmaceutically acceptable carrier.

[23] The invention also comprisies use of a compound according to group [21] in therapy and to a method of treating a patient in need of treatment thereof comprising administering to said patient a pharmaceutically effective amount of a compound or composition according to group [21] or [22].

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the

like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. "Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of formulas (I). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group,

respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and the like.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety, depression, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a host.

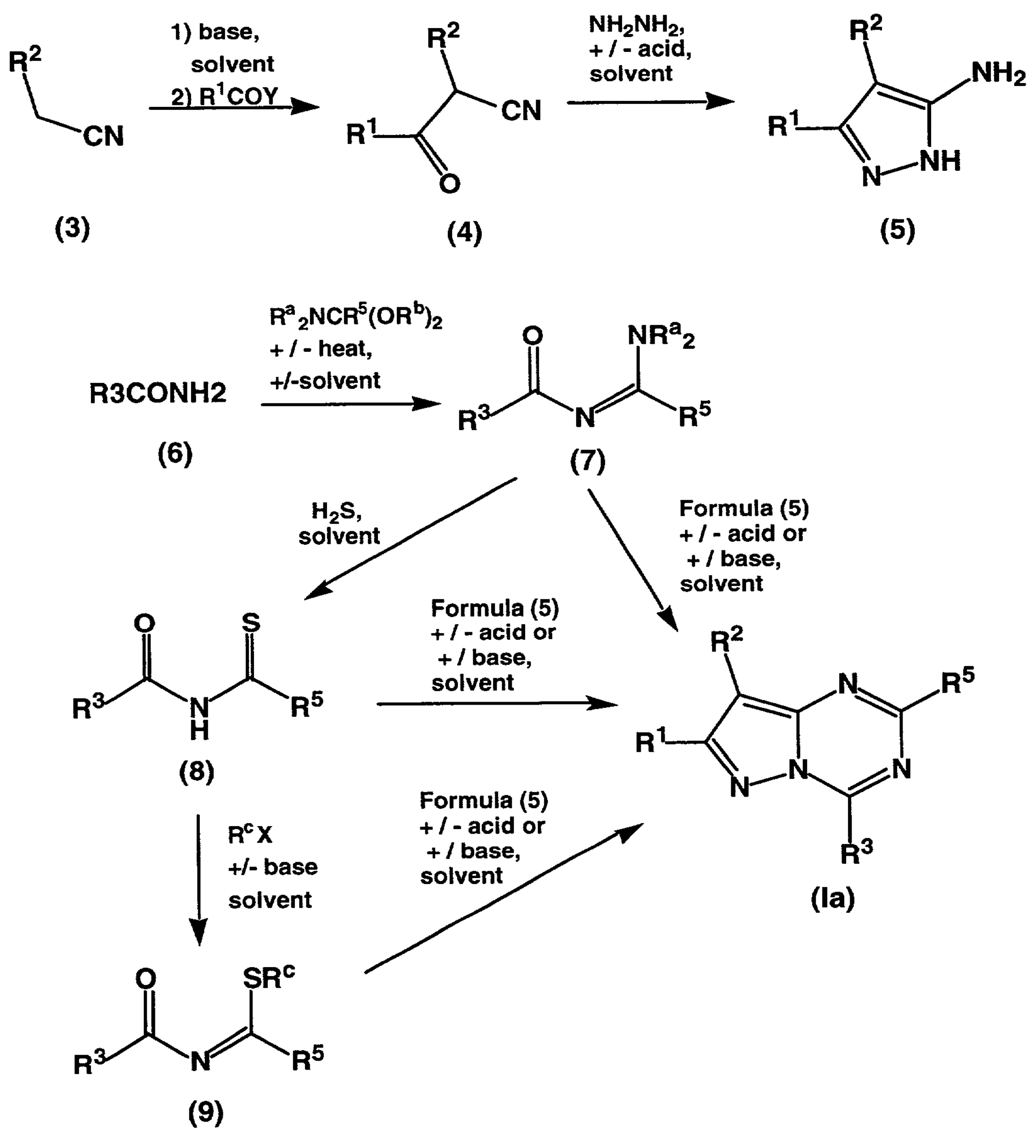
The variables as described in group [9] above are also shown in Schemes 1-4 which describe the synthesis of compounds of the invention.

Syntheses

Some compounds of Formula (Ia), may be prepared from intermediate compounds of Formula (3) using the procedures outlined in Scheme 1 with the variables defined as above. Compounds of Formula (3) may be treated with a base in an inert solvent, followed by reaction with compounds of the Formula R^1COY, where R^1 is defined above and Y is a halogen, alkoxy, dialkylamino, alkylthio, alkanoyloxy, alkanesulfonyloxy or cyano group. Bases may include, but are not limited to, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably

Scheme 1



dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 100°C. The resulting intermediates (4) are then reacted with hydrazine or its hydrate in an inert solvent in the presence or absence of an acid to provide pyrazoles (5). Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Preferred temperatures range from ambient temperature to 150°C.

Compounds of Formula (Ia) may be prepared by reaction of pyrazoles (5) with intermediates (7), or (8) or (9) in the presence or absence of an acid or base in an inert solvent. Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-

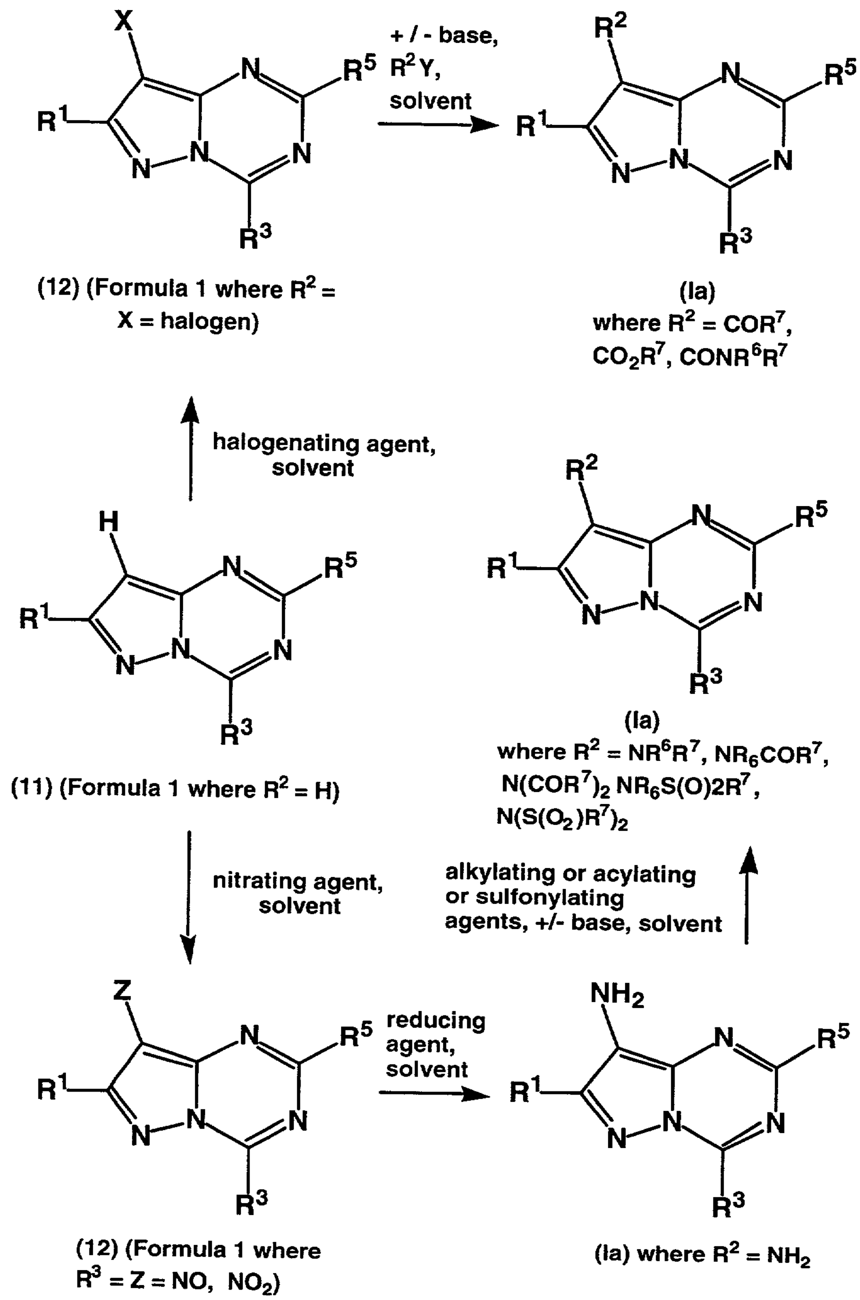
dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Preferred temperatures range from ambient temperature to 150°C. Intermediates (7), (8) and (9) are derived from amides (6). Amides (6) may be reacted in an inert solvent in the presence or absence of an acid with compounds of the Formula $R^a{}_2NCR^5(OR^b)_2$, where R^a and R^b independently are lower alkyl, to generate compounds of Formula (7). Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid),

alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used. Preferred temperatures range from ambient temperature to 150°C. Intermediates of Formula (7) may be converted to compounds of Formula (8) by reaction with H_2S in an inert solvent. Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid, phosphoric acid or cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane). Compounds of Formula (8) may be converted to compounds of Formula (9) by treatment with a base and an alkylating agent in an inert solvent at reaction temperatures ranging from -80°C to 250°C. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably N,N-di-isopropyl-N-ethyl amine or triethyl amine) or aromatic amines (preferably pyridine). Alkylating agents may include, but are not limited to, C_1-C_{10} alkyl -halides, -tosylates, -mesylates or -triflates or C_1-C_{10} haloalkyl(1 - 10 halogens)-halides, -tosylates, -mesylates or -triflates. Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides

(preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 100°C.

Compounds of Formula (Ia) may also be prepared by the methods shown in Scheme 2. Compounds of Formula (11) may be treated with a halogenating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (12) (where X is halogen). Halogenating agents include, but are not limited to, Br_2, Cl_2, I_2, N-bromosuccinimide, N-iodosuccinimide or N-chlorosuccinimide. Bases may include, but are not limited to, alkali metal carbonates, alkali metal bicarbonates, trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -20°C to 150°C. Compounds of Formula (12) may then

Scheme 2



be reacted with a base or a metal in the presence or absence of a metal salt in an inert solvent and then treated with a compound of the Formula R^2Y where Y is halogen, alkoxy, dialkylamino, alkylthio, alkanoyloxy, alkanesulfonyloxy or cyano groups. Examples of bases include, but are not limited to, alkyl or aryl lithiums

(e.g. n-butyl lithium or t-butyl lithium) or alkyl alkaline earth metal halides (e.g. MeMgBr). Examples of metals, include but are not limited to, alkali metals (e.g. Li) or alkali earth metals (e.g. Mg). Examples of metal salts include, but are not limited to, alkali metal halides, alkaline earth halides or transition metal halides such as $ZnCl_2$, $CeCl_3$ or CuI. Inert solvents may include, but are not limited todialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), alkanes or aromatic hydrocarbons (preferably benzene or toluene. Preferred reaction temperatures range from -100°C to 100°C.

Some compounds of Formula (Ia), where R^2 = NR^8COR^7, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^8CO_2R^{13}$ or NR^6R^7, may be prepared from intermediate compounds of Formula (11) (Formula (Ia) where R^2 = H), using the procedures also outlined in Scheme 2. Compounds of Formula (11) may be treated with a nitrating or nitrosating agent in the presence or absence of an acid in an inert solvent at reaction temperatures ranging from -80°C to 250°C to give products of Formula (12) (where Z = NO or NO_2). Examples of nitrating agents include, but are not limited to, nitric acid, nitrous acid, alkali metal nitrates or nitrites (e.g. KNO_3 or KNO_2) or alkyl nitrites (e.g. isoamyl nitrite). Acids include, but are not limited to, alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloacetic acids (e.g. trifluoroacetic acid), alkyl-, haloalkyl- or aryl-sulfonic acids (e.g. trifluoromethanesulfonic acid, p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), alkanes, dialkyl ethers (preferably glyme or diglyme), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Compounds of Formula (12) may then be treated with a reducing agent in an

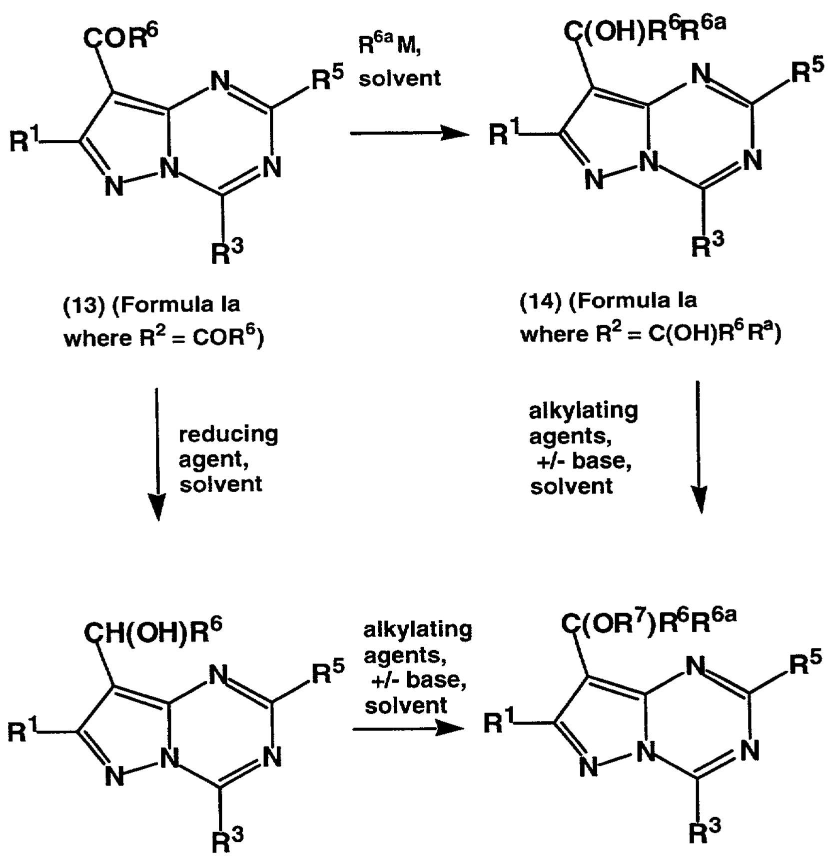
inert solvent to provide compounds of Formula (1), where $R^2 = NH_2$. Reducing agents include, but are not limited to, (a) hydrogen gas in combination with noble metal catalysts such as Pd-on-carbon, PtO_2, Pt-on-carbon, Rh-on-alumina or Raney nickel or (b) alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane, dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides, or dialkyl aluminum hydrides (such as di-isobutylaluminum hydride). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C. Compounds of Formula (Ia), where $R^2 = NH_2$, may be converted by treatment with alkylating agents or acylating agents in the presence or absence of a base in an inert solvent to compounds of Formula (Ia), where $R^2 = NR^6COR^7$, $N(COR^7)_2$, $NR^8CONR^6R^7$, $NR^6CO_2R^7$, $N(S(O)_2R^7)_2$, $NR^6S(O)_2R^7$ or NR^6R^7. Alkylating agents may include, but are not limited to, alkyl-halides, -tosylates, -mesylates or -triflates; C_3-C_{10} alkenyl-halides, -tosylates, -mesylates or -triflates; ; C_3-C_{10} alkynyl-halides, -tosylates, -mesylates or -triflates; C_3-C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4-C_{12} cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; C_5-C_{10} cycloalkenyl-halides, -tosylates, -mesylates or -triflates; or C_6-C_{14} cycloalkenyl-halides, -tosylates, -mesylates or -triflates. Each of the above alkylating agents may be optionally substituted in a way consistent with the definition of R^2. Acylating agents may include, but are not limited to, acyl halides or anhydrides. Sulfonylating agents include, but are not limited to, sulfonyl halides or anhydrides. Each of the above acylating or sulfonylating agents may be optionally

substituted in a way consistent with the definition of R^2. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -70 °C to 100°C.

Compounds of Formula (Ia), where $R^2 = CR^6(OR^7)R^{6a}$, may be prepared by the procedures shown in Scheme 3. Compounds of Formula (13) (Formula 1 where $R^3 = COR^6$) may be reacted with reagents of the Formula $R^{6a}M$ in an inert solvent, where R^{6a} is defined above and M is alkali metal, ZnCl, ZnBr, ZnI, MgBr, MgCl, MgI, $CeCl_2$, or $CeBr_2$. Inert solvents may include, but are not limited to, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -70 °C to 100°C. The resulting intermediates (15) (Formula (Ia) where $R^2 = CR^6(OH)R^{6a}$) may then be reacted with an alkylating agent in the absence or presence of a base in an inert solvent. Alkylating agents may include, but are not limited to, alkyl-halides, -tosylates, -mesylates or -triflates; C_3-

C_{10} alkenyl-halides, -tosylates, -mesylates or -triflates; ; C_3-C_{10} alkynyl-halides, -tosylates, -mesylates or -triflates; C_3-C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4-C_{12} cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; C_5-C_{10} cycloalkenyl-halides, -tosylates, -mesylates or -triflates; or C_6-C_{14} cycloalkenyl-halides, -tosylates, -mesylates or -triflates. Each of the above alkylating agents may be optionally substituted in a way consistent with the definition of R^2. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably

Scheme 3



pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -70 °C to 100°C.

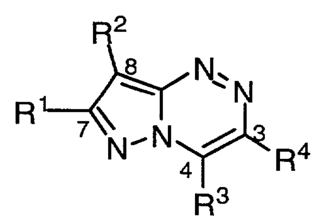
Alternatively, compounds of Formula (Ia), where $R^2 = CR^6(OR^7)R^{6a}$, may be prepared by other procedures shown in Scheme 3. Compounds of Formula (13) (Formula Ia where $R^2 = COR^6$) may be treated with a reducing agent in an inert

solvent to afford intermediates of Formula (15) (Formula (Ia) where R^2 = CHR^6OH). Reducing agents include, but are not limited to, (a) hydrogen gas in combination with noble metal catalysts such as Pd-on-carbon, PtO_2, Pt-on-carbon, Rh-on-alumina or Raney nickel or (b) alkali metal or alkaline earth metal borohydrides (preferably lithium or sodium borohydride), borane, dialkylboranes (such as di-isoamylborane), alkali metal aluminum hydrides (preferably lithium aluminum hydride), alkali metal (trialkoxy)aluminum hydrides, or dialkyl aluminum hydrides (such as di-isobutylaluminum hydride). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 6 carbons), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -80°C to 100°C. Intermediates of Formula Formula (15) (Formula (Ia) where R^2 = CHR^6OH)) may then be reacted with an alkylating agent in the presence or absence of a base in an inert solvent. Alkylating agents may include, but are not limited to, alkyl-halides, -tosylates, -mesylates or -triflates; C_3-C_{10} alkenyl-halides, -tosylates, -mesylates or -triflates; ; C_3-C_{10} alkynyl-halides, -tosylates, -mesylates or -triflates; C_3-C_6 cycloalkyl-halides, -tosylates, -mesylates or -triflates; C_4-C_{12} cycloalkylalkyl-halides, -tosylates, -mesylates or -triflates; C_5-C_{10} cycloalkenyl-halides, -tosylates, -mesylates or -triflates; or C_6-C_{14} cycloalkenyl-halides, -tosylates, -mesylates or -triflates. Each of the above alkylating agents may be optionally substituted in a way consistent with the definition of R^2. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium

bis(trimethylsilyl)amide), trialkyl amines (prefereably di-isopropylethyl amine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from -70 °C to 100°C.

In addition to the specific and generic groups on compounds Ia as shown above in Schemes 1-3, the additional compounds within the generic scope having a compound of formula Ia with R^1-R^5 as described or recited in group [1] may be made according to the general procedures described in these schemes using the appropriate starting materials and as described in the specific examples as well.

The embodiment of this invention concerning compounds of Formula (Ib) with the structure

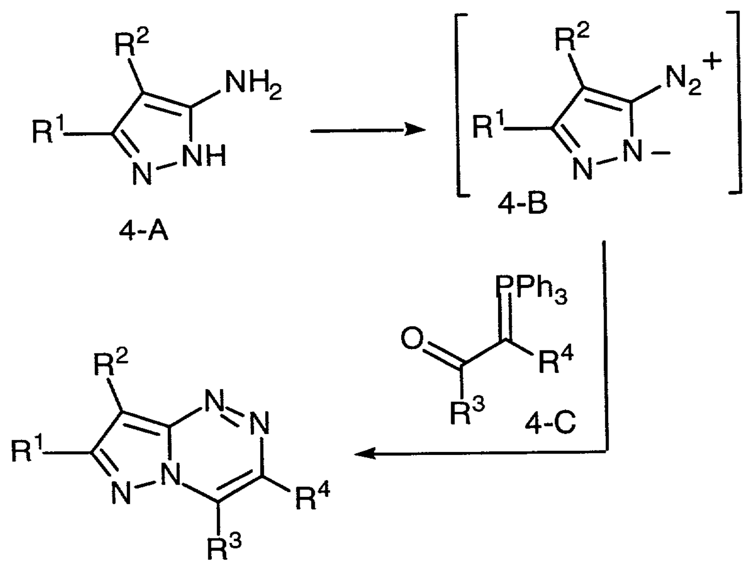


may be prepared according to the following method:

The method of Ege and Gilbert, *J. Het. Chem.* **1981**, *18*, 675-677, is used to prepare the desired ring system (Scheme 4). Thus, aminopyrazole **4-A** is converted to diazonium salt **4-B**, using sodium nitrite/acid or such reagents as isoamylnitrite. The diazonium salt is

condensed with a phosphorus ylide compound **4-C** to give the pyrazolo[5,1-*c*][1,2,4]triazine product.

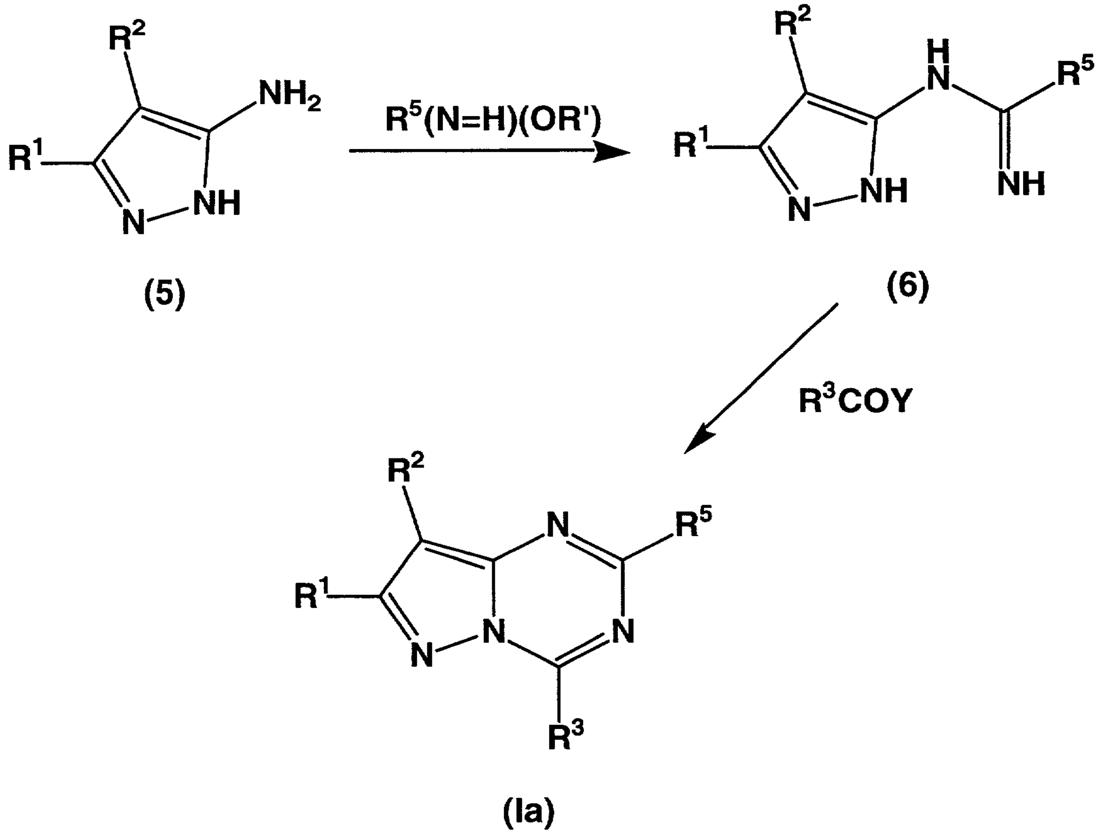
<u>Scheme 4</u>



Some compounds of Formula (Ia), may be prepared from intermediate compounds of Formula (3) using the procedures outlined in Scheme 5 with the variables defined as above. Compounds of Formula (5) may be treated with compounds of the Formula R^5(N=H)(OR′), where R′ is lower alkyl or their acid- addition salts, in the presence or absence of a base in an inert solvent. Bases may include, but are not limited to, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-

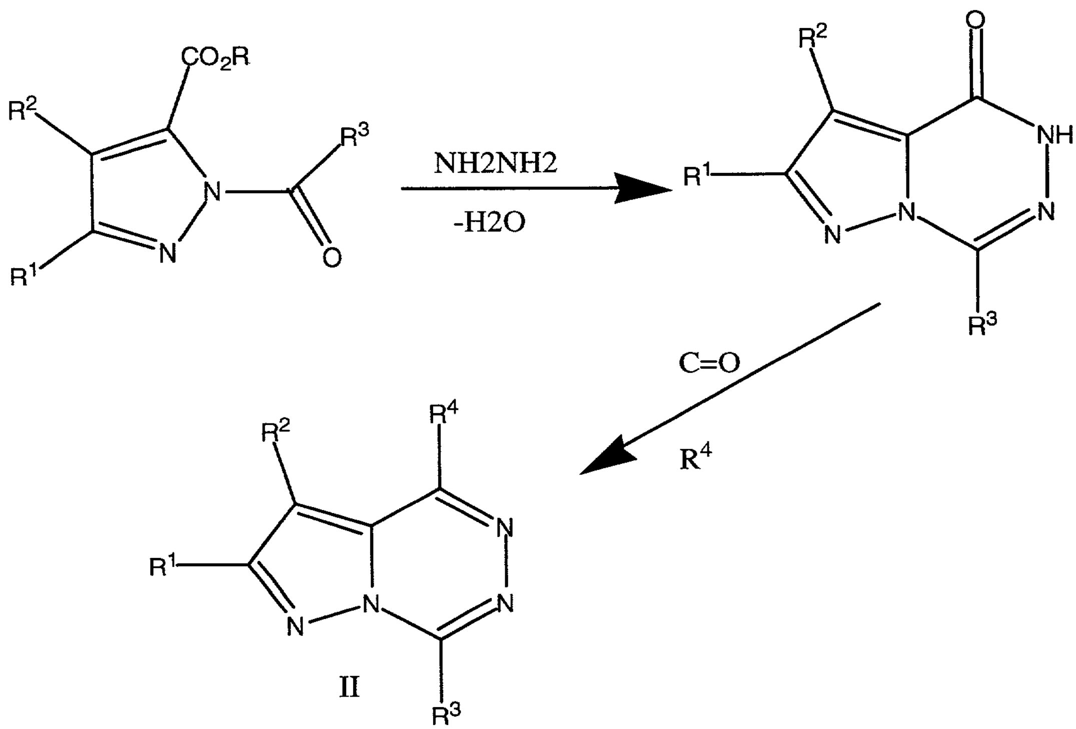
dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 100°C. The resulting intermediates are then treated with compounds of the Formula R3COY, where Y is halogen or lower alkoxy, in the presence or absence of a base in an inert solvent to provide compounds of the Formula (Ia). Bases may include, but are not limited to, alkyl lithiums, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine). Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from -80°C to 100°C.

SCHEME 5



Compounds of formula II as described above are also readily prepared according to the general procedure described in Scheme 6. This procedure is described generally in *J. Het. Chem* **1981**, 1319.

SCHEME 6



II

The following specific synthetic examples describe the procedures described generically above which, when applied to appropriately substituted substrates, were and may be employed in the synthesis of the compounds in Table 1.

<u>EXAMPLES</u>

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on an Varian FT-NMR (300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethysilane standard in deuterochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were recorded on a Finnegan MAT 8230 spectrometer (using chemi-ionization (CI) with NH_3 as the carrier gas or gas

chromatography (GC) as specified below) or a Hewlett Packard 5988A model spectrometer. Melting points were recorded on a Buchi Model 510 melting point apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper.

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to the general procedures outlined by D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., (New York: Pergamon Press, 1988). Chromatography (thin layer (TLC) or preparative) was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight.

EXAMPLE 1 4-(2,4-dichlorophenyl)-8-(3-pentyl)-7-ethyl-2-methyl-pyrazolo[1,5-a]-1,3,5-triazine (Formula Ia, R^1 is ethyl, R^5 is methyl, R^2 is 3-pentyl, R^3 is 2,4-dichlorophenyl).

A. N-(1-(Dimethylamino)ethylidene)-2,4-dichlorobenzamide

A mixture of 2,4-dichlorobenzamide (1.9 g, 10 mmol) and N,N-dimethylformamide dimethyl acetal (3.5 g, 3.8 mL, 26 mmol) was heated at 120 °C and stirred under a nitrogen atmosphere for 2 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo to afford an oil. Medium pressure chromatography on silica gel (EtOAc:hexanes::1:3 to 1:1) and removal of solvent *in vacuo* afforded a solid (2.03 g, 78% yield): NMR ($CDCl_3$,300 MHz): δ 7.73 (d, 1H, J = 8), 7.39 (d, 1H, J = 2), 7.24 (dd, 1H, J = 8,2), 3.16 (s, 3H), 3.13 (s, 3H), 2.39 (s, 3H).

B. N-(Thioacetyl)-2,4-dichlorobenzamide

Hydrogen sulfide was bubbled through glacial acetic acid (20 mL) for approximately 5 min. The above intermediate was added portionwise over 5 min. Additional hydrogen sulfide was bubbled through the reaction mixture for approximately 10 min. Nitrogen was then bubbled through the reaction mixture. Dilution with water (25 mL) caused a precipitate to form. The solid was collected by filtration, washed with copious amounts of water and dried in vacuo. The resulting solid (1.75 g, 90% yield) was used without further purification: NMR ($CDCl_3$,300 MHz): δ 9.9 (br s, 1H), 7.68 (d, 1H, J = 8), 7.51 (d, 1H, J = 2), 7.40 (dd, 1H, J = 9,2), 3.10 (s, 3H).

C. 3-Amino-5-ethyl-4-(3-pentyl)pyrazole

A mixture of NaCN (4.1 g, 82.7 mmol) and KI (154 mg, 0.9 mmol) in anhydrous dimethylsulfoxide (40 mL) was heated to 40 oC with stirring. 3-Ethyl-1-bromobutane (12.4 g, 75.2 mmol) was added dropwise over 10 min. The reaction mix was first heated to 80 oC and stirring was continued for 1h, then to 120 oC and stirred for 5h. The reaction mix was cooled to ambient temperature and a precipitate formed. Dilution with water (150 mL), extraction with ether (3 X 100 mL), washing the combined organic layers with a saturated NaCl solution, drying over MgSO4 and filtration afforded a solution. Removal of solvent in vacuo provided 3-ethylpentanenitrile (7.4 g, 89% yield): NMR ($CDCl_3$,300 MHz): δ 2.33 (d, 2H, J = 6), 1.45-1.40 (m, 5H), 0.92 (t, 6H, J = 7).

A solution of di-isopropylamine (14.8 g, 20.5 mL, 147 mmol) in anhydrous THF (40 mL) was cooled to -78 oC with stirring under a nitrogen atmosphere. A solution of n-butyl lithium in hexanes (1.6M, 87.5 mL, 140 mmol) was added dropwise over 15 min. The resulting solution was stirred for an additional 30 min. A solution of 3-ethylpentanenitrile (7.4 g, 67 mmol) in THF (30 mL) was added dropwise over 15 min and then the reaction mixture

was stirred for 30 min. A solution of ethyl propionate (6.8 g, 7.6 mL, 67 mmol) in THF (20 mL) was added dropwise; then the reaction mixture was warmed with stirring to ambient temperature over 3 h. The mix was poured onto water (200 mL) and the pH was adjusted to ~ 4 by the slow addition of a concentrated Hcl solution. Three extractions with ether (100 mL), drying the combined organic layers over MgSO4, filtration and removal of solvent in vacuo provided an oil (9.53 g): NMR ($CDCl_3$,300 MHz): δ 3.50 (d, 1H, J = 4), 2.74 (q, 2H, J = 7), 1.85-1.75 (m, 1H), 1.45-1.35 (m, 4H), 1.12 (t, 3H, J = 7), 1.0-0.8 (m, 6H).

A mixture of the above intermediate (7.0 g), hydrazine hydrate (2.30 g, 2.23 mL, 46 mmol) and glacial acetic acid (1mL) in toluene was heated to reflux temperature in a Dean-Stark apparatus and stirred for 16 h. The reaction mixture was cooled to ambient temperature and solvent was removed in vacuo. EtOAc (100 mL) was added to the residue and the resulting solution was washed three times with a saturated NaHCO3 solution (25 mL). The organic solution was dried over MgSo4, filtered and concentrated in vacuo to provide an oil (6.7 g, 88% overall yield): NMR ($CDCl_3$,300 MHz): δ 2.53 (q, 2H, J = 7), 1.70-1.50 (m, 5H), 1.20 (t, 3H, J = 7), 0.83 (t, 6H, J = 7).

D. A mixture of N-(thioacetyl)-2,4-dichlorobenzamide (200 mg, 0.81 mmol) and 3-amino-5-ethyl-4-(3-pentyl)pyrazole (146 mg, 0.81 mmol) in dioxan (1 mL) was stirred at reflux temperature for 16 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo. Preparative TLC using EtOAc:hexanes::1:1 generated the title product (77.3 mg, 24% yield): mp = 91-93 oC; NMR ($CDCl_3$,300 MHz): δ 7.64 (d, 1H, J = 8), 7.57 (d, 1H, J = 2), 7.44 (dd, 1H, J = 8,2), 2.77 (q, 2H, J = 8), 2.69 (s, 3H), 2.80-2.60 (m, 1H), 2.00-1.80 (m, 4H), 1.25 (t, 3H, J = 8), 0.82 (t, 6H, J = 7); CI-HRMS m/z Calcd: 377.1294, Found: 377.1303.

EXAMPLE 1a 4-(2,4-dichlorophenyl)-8-(3-pentyl)-7-ethyl-2-methyl-pyrazolo[1,5-a]-1,3,5-triazine

Alternate Preparation of (Formula Ia, R^1 is ethyl, R^5 is methyl, R^2 is 3-pentyl, R^3 is 2,4-dichlorophenyl)

A. N-(1-(Methylthio)ethylidene)-2,4-dichlorobenzamide

A mixture of N-(thioacetyl)-2,4-dichlorobenzamide (400 mg, 1.6 mmol) and K2CO3 (445 mg, 3.22 mmol) in anhydrous acetonitrile (20 mL) was stirred at ambient temperature. Iodomethane (458 mg, 0.2 mL, 3.22 mmol) was added and the reaction mixture was then stirred for 2.5 h. Solvent was removed in vacuo and the residue was partitioned between ether and water. The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo to give an oil (406 mg): NMR ($CDCl_3$,300 MHz): δ 7.86 (d, 1H, J = 8), 7.47 (d, 1H, J = 2), 7.32 (dd, 1H, J = 8, 2), 2.40 (s, 3H), 2.29 (s, 3H).

B. A mixture of N-(1-(methylthio)ethylidene)-2,4-dichlorobenzamide (100 mg, 0.38 mmol) and 3-amino-5-ethyl-4-(3-pentyl)pyrazole (69 mg, 0.38 mmol) in dioxan (1 mL) was stirred at reflux temperature for 2 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo. Preparative TLC using EtOAc:hexanes::1:1 generated the title product (68 mg, 47% yield), which was identical to the product obtained by the method described in Example 1.

EXAMPLE 2 4-(2,4-dichlorophenyl)-8-diethylamino-7-ethyl-2-methyl-pyrazolo[1,5-a]-1,3,5-triazine

(Formula 1, R^1 is ethyl, R^5 is methyl, R^2 is diethylamino, R^3 is 2,4-dichlorophenyl)

A. 4-(2,4-dichlorophenyl)-7-ethyl-2-methyl-pyrazolo[1,5-a]-1,3,5-triazine

A mixture of 3-amino-5-ethylpyrazole (10.3 g, 39.3 mmol) and N-(1-(methylthio)ethylidene)-2,4-dichlorobenzamide (4.0 g, 35.7 mmol) in anhydrous dioxan (20 mL) was stirred at reflux temperatrue under a nitrogen atmosphere for 16 h. After being cooled to ambient temperature, the reaction mix was concentrated in vacuo and the residue was treated with dichloromethane. The resulting supsension was filtered and the filtrate was concentrated in vacuo to afford an oil (1.5 g, 14 % yield): NMR ($CDCl_3$,300 MHz): δ 7.62 (d, 1H, J = 8), 7.59 (d, 1H, J = 2), 7.45 (dd, 1H, J = 8,2), 6.42 (s, 1H), 2.82 (q, 2H, J = 8), 2.73 (s, 3H), 1.30 (t, 3H, J = 8).

B. 4-(2,4-dichlorophenyl)-7-ethyl-2-methyl-8-nitro-pyrazolo[1,5-a]-1,3,5-triazine

A solution of 4-(2,4-dichlorophenyl)-7-ethyl-2-methyl-pyrazolo[1,5-a]-1,3,5-triazine (653 mg, 2.2 mmol) in acetic anhydride (4 mL) was cooled with stirring to -5 to -10 oC. A solution of fuming nitric acid (160 mg, 2.55 mmol) in acetic anhydride (2 mL) was added dropwise over 15 min. The reaction mixture was stirred at the same temperature for 3 h, then it was partitioned between water and ether three times. The combined organic layers were washed with a saturated NaHCO3 solution, dried over MgSO4 and filtered. Solvent was removed in vacuo to provide a solid. Column chromatography (EtOAc:hexanes::1:9 to 1:4) provided a solid (166 mg, 21% yield) after removal of solvent in vacuo: NMR ($CDCl_3$,300 MHz): δ 7.64 (d, 1H, J = 8), 7.63 (d, 1H, J = 2), 7.50 (dd, 1H J = 8, 2), 3.19 (q, 2H, J = 7), 2.94 (s, 3H), 1.32 (t, 3H, J = 7).

B. 4-(2,4-dichlorophenyl)-7-ethyl-2-methyl-8-amino-pyrazolo[1,5-a]-1,3,5-triazine

A mixture of the above intermediate (160 mg, 0.45 mmol), Na2S2O4 (554 mg, 3.2 mmol), concentrated ammonium hydroxide (0.1 mL) in dioxan (8 mL) was stirred at ambient temperature for 30 min. The reaction mixture was concentrated in vacuo and the residue was partitioned between ether and water three times. The organic layers were combined, dried over MgSO4, filtered and concentrated in vacuo to give a solid (92.5 mg, 64% yield): NMR ($CDCl_3$,300 MHz): δ 7.60 (d, 1H, J = 8), 7.57 (d, 1H, J = 2), 7.43 (dd, 1H, J = 8,2), 2.79 (q, 2H, J = 8), 2.63 (s, 3H), 1.30 (t, 3H, J = 8)

C.

A mixture of the above intermediate (46 mg, 0.14 mmol), ethyl triflate (64 mg, 46 µL, 0.36 mmol) and i-Pr2NEt (46 mg, 62 µL, 0.36 mmol) in dichloromethane (1 mL) was stirred at room temperature for 2h. Solvent was removed in vacuo. Column chromatography (EtOAc:hexanes::1:9) generated the title compound, a solid (30.1 mg, 57% yield): mp = 98-99 oC: NMR ($CDCl_3$,300 MHz): δ 7.63 (d, 1H, J = 8), 7.57 (d, 1H, J = 2), 7.44 (dd, 1H, J = 8, 2), 3.22 (q, 4H, J = 7), 2.77 (q, 2H, J = 8), 2.69 (s, 3H), 1.25 (t, 3H, J = 8), 1.00 (t, 6H, J = 8); CI-HRMS m/z Calcd: 378.1252; Found: 378.1274.

Using the above procedures and modifications known to one skilled in the art of organic synthesis, the following examples of Table 1 were or may be prepared. The examples delineated in Table 1 may be prepared by the methods outlined in Examples 1, 2 or 3 or combinations thereof. Commonly used abbreviations are: Ph is phenyl, Pr is propyl, Me is methyl, Et is ethyl, Bu is butyl, Ex is Example, amorph. is amorphous. In Table 1, unless otherwise indicated, the examples with the physical data shown are based upon structure Ic. Example 10, described below, shows a detailed preparation of a 1,2,4 triazine. Table 1 also shows the preferred examples having

structures Ie and If that can readily be made according to the procedure delinated below for Example 10.

Example 10 4-(2,4-dichlorophenyl)-7-ethyl-8-(3-pentyl)pyrazolo[5,1-c][1,2,4]triazine

Part A. A mixture of 2-ethyl-1-bromobutane (10.0 mL, 71.4 mmol), potassium cyanide (14.0 g, 215 mmol) and aliquat 336 (10 drops) in 50 mL water was heated to reflux overnight with vigorous stirring. The mixture was cooled, and extracted with dichloromethane (2 x 50 mL). The extracts were combined, dried over magnesium sulfate, filtered and evaporated. The residual liquid was distilled bulb-to-bulb to afford pure product, 3-ethylpentanenitrile (5.50 g, 49.5 mmol, 69%). b.p. 40-45 °C (5 mm Hg). Spectral data: ^1H NMR (300 MHz, $CDCl_3$): δ 2.33 (2H, d, J = 5.8 Hz), 1.62-1.36 (5H, m), 0.92 (6H, t, J = 7.3 Hz). MS (H_2O-GC/MS): *m/e* 112 (100).

Part B. A solution of diisopropylamine (7.50 mL, 57.2 mmol) in THF (100 mL) was cooled to -78 °C, and treated with n-butyllithium (34.0 mL of a 1.6 M solution in hexane). The solution was warmed briefly to 0 °C, and then recooled to -78 °C. The nitrile compound from Part A was then added by syringe, and the solution was allowed to stir for 1 hour. Then, ethyl propionate (6.50 mL, 56.7 mmol) was added by syringe, and the resulting mixture was allowed to stir and warm to ambient temperature for 12 hours. It was poured into 200 mL of satd. aq. NH_4Cl solution, and this was extracted with ethyl acetate (2 x 200 mL). The extracts were combined, dried over magnesium sulfate, filtered and evaporated. The residual oil was separated

by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to afford the product, 4-cyano-5-ethyl-3-heptanone, as an oil 4.06 g, 24.3 mmol, 49%). TLC R_F 0.47 (20:80 ethyl acetate-hexane). Spectral data: ^1H NMR (300 MHz, $CDCl_3$): δ 3.49 (1H, d, J = 4.4 Hz), 2.74 (2H, q, J = 7.3 Hz), 2.08-1.98 (1H, m), 1.70-1.58 (1H, m), 1.50-1.20 (3H, m), 1.12 (3H, t, J = 7.3 Hz), 0.95 (3H, t, J = 7.3 Hz), 0.91 (3H, t, J = 7.3 Hz). MS (H_2O-GC/MS): *m/e* 167 (100).

Part C. A solution of the ketonitrile from Part B (4.06 g, 24.3 mmol), hydrazine hydrate (2.70 mL, 55.7 mmol) and acetic acid (5.00 mL, 83.7 mmol) in benzene (50 mL) was heated to reflux under a Dean-Stark trap with azeotropic distillation of water. After being heated for 12 hours, the mixture was cooled and poured into 100 mL 1 N aq. $NaHCO_3$ solution. This was extracted with ethyl acetate (2 x 100 mL), and the extracts were washed in sequence with brine, combined, dried over sodium sulfate, filtered and evaporated to afford sufficiently-pure product, 3-amino-5-ethyl-4-(3-pentyl)pyrazole, as a viscous oil (2.48 g, 13.7 mmol, 56%). Spectral data: ^1H NMR (300 MHz, $CDCl_3$): δ 3.48 (2H, br), 2.54 (2H, q, J = 7.3 Hz), 2.25-2.14 (1H, m), 1.71-1.49 (4H, m), 1.20 (3H, t, J = 7.3 Hz), 0.83 (6H, t, J = 7.3 Hz), 1H missing. MS (NH_3-CI): *m/e* 183 (12), 182 (100).

Part D. A solution of 3-amino-5-ethyl-4-(3-pentyl)pyrazole (0.750 g, 4.14 mmol) was suspended in 4 mL water and made acidic with conc. aq. HCl (2 mL). This was cooled in an ice bath, and a conc. aq. solution of sodium nitrite (0.286 g, 4.14 mmol) was added dropwise. After stirring for 30 min., the mixture was diluted with

ice-cold dichloromethane (40 mL) and made alkaline with a saturated solution of sodium carbonate in water. The organic layer was separated, dried over sodium sulfate and filtered. The filtrate was then delivered dropwise to a stirring solution of 2,4-dichlorobenzoyl)methylenetriphenylphosphorane (Bauer, et al., *J. Het. Chem.* **1998**, *35*, 81-87) (1.86 g, 4.14 mmol) in dichloromethane at 10 °C. After stirring for 10 hrs. with warming to ambient temperature, the reaction mixture was evaporated, and the residual material was separated by column chromatography (silica gel, 15:85 ethyl acetate-hexane) to afford the title product (0.124 g, 8.2%) as orange crystals (m.p. 116.7-117.8 °C). TLC R_f 0.51 (20:80 ethyl acetate-hexane).

This procedure can be utilized to make compounds of formula Ib having the variables as defined in group [1] above by appropriately substituting or preparing any of the different variables for R^1, R^2, R^3, R^4 including substituted versions thereof as defined in group [1] or any of the more preferred groups.

Example 11

4-phenyl-8-(3-pentyl)-7-ethyl-2-methyl-pyrazolo[1,5-a]-1,3,5-triazine (Formula Ia, R^1 is ethyl, R^5 is methyl, R^2 is 3-pentyl, R^3 is phenyl).

Ethyl acetimidate hydrochloride (656 mg, 5.31 mmol) was added to a solution of K_2CO_3 (734 mg, 5.31 mmol) in H_2O (2 mL) in a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL) to form the free base. The combined organic layers were dried with Na_2SO_4, and filtered through a plug of cotton. The CH_2Cl_2 extract was transferred directly into a 15 mL round bottom flask containing of 3-amino-5-ethyl-4-(3-pentyl)pyrazole (300 mg, 1.77 mmol). Acetonitrile (1.5 mL, anhydrous) was

added followed by HOAc (0.112 mL, 1.95 mmol) and the mixture was stirred overnight at room temperature. The solid was collected by filtration to give 358 mg (96% yield) of 3-acetamidino-5-ethyl-4-(3-pentyl)pyrazole, hydrochloride salt as a white solid: mp = 168.5-171.5 °C, ^{1}H NMR, 300 MHz (D_2O) δ 2.51 (q, *J* = 7.7 Hz, 2 H), 2.24 (s, 3 H), 2.21 - 2.15 (m, 1 H), 1.72 (s, 3 H), 1.52 - 1.43 (m, 2 H), 1.33 - 1.22 (m, 2 H), 1.02 (t, *J* = 7.7 Hz, 3 H), 0.56 (t, *J* = 7.3 Hz, 6 H), CI-MS (NH_3) *m/e* 223.2 [$(M + H - HOAc)^+$; calcd for $C_{12}H_{23}N_4$: 223.2].

To a solution of K_2CO_3 (48 mg, 0.35 mmol) in H_2O (3 mL) in a separatory funnel was added 3-acetamidino-5-ethyl-4-(3-pentyl)pyrazole, hydrochloride salt (60 mg, 0.212 mmol). The aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the free base of the pyrazole (39 mg, 0.175 mmol). This intermediate (39 mg, 0.175 mmol) was dissolved in dioxane (1 mL) and a solution of benzoyl chloride (30 mg, 0.210 mmol) in dioxane (1 mL) was added via cannula followed by the addition of a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred at room temperature for 15 min (turned cloudy then clear) and was subsequently heated at reflux (112 °C) for 15 h. The mixture was cooled to room temperature and concentrated. The residue was purified via preparative thin layer chromatography (silica gel, 1 mm thickness) using 20% EtOAC in hexanes to give 29 mg (54% yield) of the title compound as a yellow oil: R_f = 0.66, ^{1}H NMR, 300 MHz ($CDCl_3$) δ 8.75 - 8.71 (m, 2 H), 7.64 - 7.53 (m, 3 H), 2.85 (q, *J* = 7.7 Hz, 2 H), 2.72 - 2.62 (m, 1 H), 2.70 (s, 3 H), 1.97 - 1.76 (m, 4 H), 1.37 (t, *J* = 7.6 Hz, 3 H), 0.82

(t, J = 7.3 Hz, 6 H), LRMS (CI, NH_3) m/e 309.2 [$(M + H)^+$; calcd for $C_{19}H_{25}N_4$: 309.2].

Example 12

4-phenyl-8-(3-pentyl)-7-ethyl-2-methyl-pyrazolo[1,5-a]-1,3,5-triazine (Formula Ia, R^1 is ethyl, R^5 is methyl, R^2 is 3-pentyl, R^3 is 2-methyl-4-chlorophenyl).

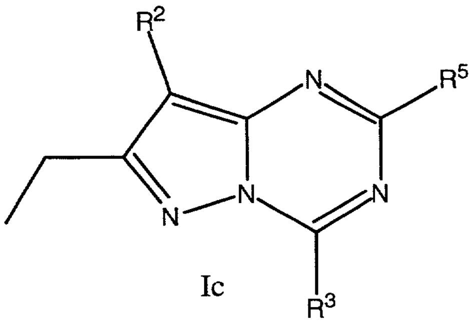
To a solution of K_2CO_3 (48 mg, 0.35 mmol) in H_2O (3 mL) in a separatory funnel was added 3-acetamidino-5-ethyl-4-(3-pentyl)pyrazole, hydrochloride salt (49 mg, 0.174 mmol). The aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the free base of **2** (31 mg, 0.139 mmol). This intermediate was dissolved in dioxane (1 mL) and a solution of 4-chloro-2-methylbenzoyl chloride (32 mg, 0.167 mmol) in dioxane (1 mL) was added via cannula followed by the addition of a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred at room temperature for 15 min (turned cloudy then clear) and was subsequently heated at reflux (112 °C) for 15 h. The mixture was cooled to room temperature and concentrated. The residue was purified via preparative thin layer chromatography (silica gel, 1 mm thickness) using 10% EtOAC in hexanes to give 14 mg (28% yield) of the title compound as a yellow solid: R_f = 0.40, mp = 84.5 - 86.5 °C, ^1H NMR, 300 MHz ($CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 1 H), 7.35 (s, 1 H), 7.34 (d,J = 7.7 Hz, 1 H), 2.77 (q, J = 7.7 Hz, 2 H), 2.68 (s, 3 H), 2.67 - 2.60 (m, 1 H), 2.28 (s, 3 H), 1.97 (m, 4 H), 1.25 (t, J = 7.7 Hz, 3 H), 0.82 (t, J = 7.3 Hz, 6 H), CI-MS (NH_3) m/e 357.1 [$(M + H)^+$; calcd for $C_{20}H_{26}N_4Cl$: 357.2].

Example 13

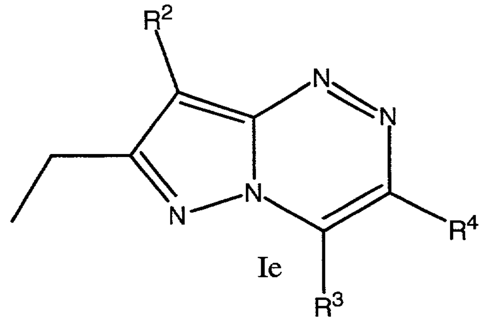
<u>4-(2-chloro-4-methylsulfonylphenyl)-8-(3-pentyl)-7-ethyl-2-methyl-pyrazolo[1,5-a]-1,3,5-triazine</u> (Formula Ia, R^1 is ethyl, R^5 is methyl, R^2 is 3-pentyl, R^3 is 2-methyl-4-methylsulfonylphenyl).

To a solution of K_2CO_3 (280 mg, 2.03 mmol) in H_2O (15 mL) in a separatory funnel was added 3-acetamidino-5-ethyl-4-(3-pentyl)pyrazole, hydrochloride salt (250 mg, 1.12 mmol). The aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the free base of 3-acetamidino-5-ethyl-4-(3-pentyl)pyrazole, hydrochloride salt (225 mg, 1.01 mmol). This intermediate was dissolved in dioxane (2 mL) and a solution of 2-chloro-4-methanesulfonylbenzoyl chloride (307 mg, 1.21 mmol) in dioxane (2 mL) was added via cannula followed by the addition of DMAP (cat.). The mixture was stirred at room temperature for 15 min (turned cloudy then clear) and was subsequently heated at reflux (112 °C) for 15 h. The mixture was cooled to room temperature and concentrated. The residue was purified via prep plate using 50% EtOAc in hexanes to give 95 mg (22% yield) of the title compound as a yellow solid: R_f = 0.61, mp = 172.3 - 173.8 °C, ^{1}H NMR, 300 MHz ($CDCl_3$) d 8.14 (d, J = 1.4 Hz, 1 H), 8.03 (dd, J = 6.6, 1.5 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 3.13 (s, 3 H), 2.78 (q, J = 7.6 Hz, 2 H), 2.70 (s, 3 H), 2.71 - 2.59 (m, 1 H), 2.00-1.77 (m, 4 H), 1.25 (t, J = 7.5 Hz, 3 H), 0.83 (t, J = 7.5 Hz, 6 H), ESI-MS *m/e* 421.0 [$(M + H)^+$; calcd for $C_{20}H_{26}N_4O_2SCl$: 421.1.

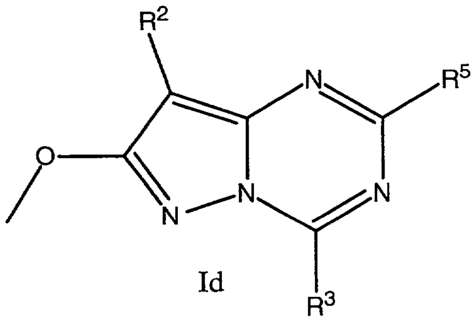
TABLE 1



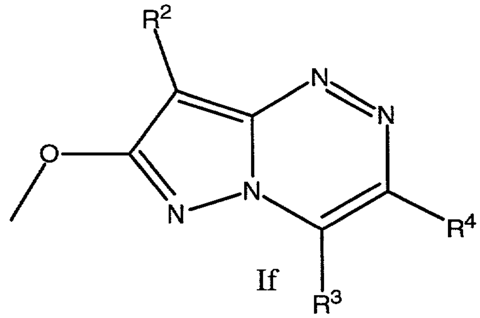
Ic



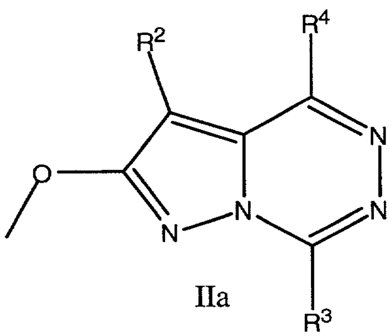
Ie



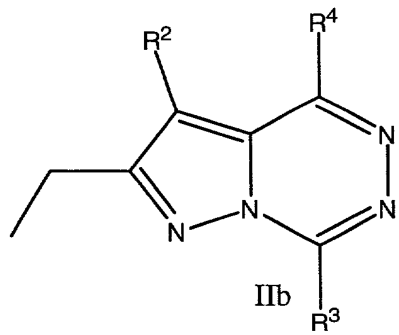
Id



If



IIa



IIb

Ex.	Formula	R^5	R^4	R^2	R^3	mp(°C)
1	Ic	Me	-	3-pentyl	2,4-Cl_2-Ph	91-93
3	Ic	Me	-	NEt_2	2,4-Cl_2-Ph	98-99
4	Ic	Me	-	3-pentyl	2-Me-4-MeO-Ph	65-67
5	Ic	Me	-	3-pentyl	2-Cl-4,5-$(MeO)_2$-Ph	104-105
6	Ic	Me	-	3-pentyl	2-Cl-4-MeO-5-F-Ph	94-97
7	Ic	Me	-	3-pentyl	2-Me-4-MeO-5-F-Ph	105-107
8	Ic	Me	-	3-pentyl	2,6-Me_2-pyrid-3-yl	oil
9	Ic	Me	-	butyl	2,4-Cl_2-Ph	amorph.
10	Ie	-	H	3-pentyl	2,4-Cl_2-Ph	-
11	Ic	Me	H	$NHCH(CH_2OMe)_2$	2,4-Cl_2-Ph	
12	Ic	Me	H	$NHCH(Et)CH_2OMe$	2,4-Cl_2-Ph	

13	Ic	Me	H	NH-2-butyl	2,4-Cl_2-Ph
14	Ic	Me	H	OCH(Et)CH_2OMe	2,4-Cl_2-Ph
15	Ic	Me	H	O-3-pentyl	2,4-Cl_2-Ph
16	Ic	Me	H	O-2-pentyl	2,4-Cl_2-Ph
17	Ic	Me	H	*R*-2-pentyl	2,4-Cl_2-Ph
18	Ic	Me	H	*S*-2-pentyl	2,4-Cl_2-Ph
19	Ic	Me	H	*R*-2-butyl	2,4-Cl_2-Ph
20	Ic	Me	H	*S*-2-butyl	2,4-Cl_2-Ph
21	Ic	Me	H	CH(Et)CH_2OH	2,4-Cl_2-Ph
22	Ic	Me	H	CH(Et)CH_2OMe	2,4-Cl_2-Ph
23	Ic	Me	H	$COCH_3$	2,4-Cl_2-Ph
24	Ic	Me	H	COEt	2,4-Cl_2-Ph
25	Ic	Me	H	CO_2Et	2,4-Cl_2-Ph
26	Ic	Me	H	CO-2-pentyl	2,4-Cl_2-Ph
27	Ic	Me	H	CO-3-pentyl	2,4-Cl_2-Ph
28	Ic	Me	H	CH(OH)CH_3	2,4-Cl_2-Ph
29	Ic	Me	H	C(OH)Me_2	2,4-Cl_2-Ph
30	Ic	Me	H	C(OH)Ph-3-pyridyl	2,4-Cl_2-Ph
31	Ic	Me	H	CH(OMe)CH_3	2,4-Cl_2-Ph
32	Ic	Me	H	CH(OMe)Et	2,4-Cl_2-Ph
33	Ic	Me	H	CH(OMe)Pr	2,4-Cl_2-Ph
34	Ic	Me	H	CH(OEt)CH_3	2,4-Cl_2-Ph
35	Ic	Me	H	CH(OPr)CH_3	2,4-Cl_2-Ph
36	Ic	Me	H	CH(OMe)Et	2,4-Cl_2-Ph
37	Ic	Me	H	CH(OMe)Pr	2,4-Cl_2-Ph
38	Ic	Me	H	cyclobutyl	2,4-Cl_2-Ph
39	Ic	Me	H	cyclopentyl	2,4-Cl_2-Ph
40	Ic	Me	H	CH(Me)cyclobutyl	2,4-Cl_2-Ph
41	Ic	Me	H	CH(OMe)cyclobutyl	2,4-Cl_2-Ph
42	Ic	Me	H	CH(Me)cyclopropyl	2,4-Cl_2-Ph
43	Ic	Me	H	CH(OMe)cyclopropyl	2,4-Cl_2-Ph
44	Ic	Me	H	CH(Et)cyclobutyl	2,4-Cl_2-Ph
45	Ic	Me	H	CH(OEt)cyclobutyl	2,4-Cl_2-Ph
46	Ic	Me	H	CH(Et)cyclopropyl	2,4-Cl_2-Ph
47	Ic	Me	H	CH(OEt)cyclopropyl	2,4-Cl_2-Ph
48	Ic	Me	H	CH(cyclobutyl)$_2$	2,4-Cl_2-Ph
49	Ic	Me	H	CH(cyclopropyl)$_2$	2,4-Cl_2-Ph
50	Ic	Me	H	NHCH(CH_2OMe)$_2$	2,4,6-Me_3-Ph

51	Ic	Me	H	NHCH(Et)CH_2OMe	2,4,6-Me_3-Ph
52	Ic	Me	H	NH-2-butyl	2,4,6-Me_3-Ph
53	Ic	Me	H	OCH(Et)CH_2OMe	2,4,6-Me_3-Ph
54	Ic	Me	H	O-3-pentyl	2,4,6-Me_3-Ph
55	Ic	Me	H	O-2-pentyl	2,4,6-Me_3-Ph
56	Ic	Me	H	*R*-2-pentyl	2,4,6-Me_3-Ph
57	Ic	Me	H	*S*-2-pentyl	2,4,6-Me_3-Ph
58	Ic	Me	H	*R*-2-butyl	2,4,6-Me_3-Ph
59	Ic	Me	H	*S*-2-butyl	2,4,6-Me_3-Ph
60	Ic	Me	H	3-pentyl	2,4,6-Me_3-Ph
61	Ic	Me	H	CH(Et)CH_2OH	2,4,6-Me_3-Ph
62	Ic	Me	H	CH(Et)CH_2OMe	2,4,6-Me_3-Ph
63	Ic	Me	H	$COCH_3$	2,4,6-Me_3-Ph
64	Ic	Me	H	COEt	2,4,6-Me_3-Ph
65	Ic	Me	H	CO_2Et	2,4,6-Me_3-Ph
66	Ic	Me	H	CO-2-pentyl	2,4,6-Me_3-Ph
67	Ic	Me	H	CO-3-pentyl	2,4,6-Me_3-Ph
68	Ic	Me	H	CH(OH)CH_3	2,4,6-Me_3-Ph
69	Ic	Me	H	C(OH)Me_2	2,4,6-Me_3-Ph
70	Ic	Me	H	C(OH)Ph-3-pyridyl	2,4,6-Me_3-Ph
71	Ic	Me	H	CH(OMe)CH_3	2,4,6-Me_3-Ph
72	Ic	Me	H	CH(OMe)Et	2,4,6-Me_3-Ph
73	Ic	Me	H	CH(OMe)Pr	2,4,6-Me_3-Ph
74	Ic	Me	H	CH(OEt)CH_3	2,4,6-Me_3-Ph
75	Ic	Me	H	CH(OPr)CH_3	2,4,6-Me_3-Ph
76	Ic	Me	H	CH(OMe)Et	2,4,6-Me_3-Ph
77	Ic	Me	H	CH(OMe)Pr	2,4,6-Me_3-Ph
78	Ic	Me	H	cyclobutyl	2,4,6-Me_3-Ph
79	Ic	Me	H	cyclopentyl	2,4,6-Me_3-Ph
80	Ic	Me	H	CH(Me)cyclobutyl	2,4,6-Me_3-Ph
81	Ic	Me	H	CH(OMe)cyclobutyl	2,4,6-Me_3-Ph
82	Ic	Me	H	CH(Me)cyclopropyl	2,4,6-Me_3-Ph
83	Ic	Me	H	CH(OMe)cyclopropyl	2,4,6-Me_3-Ph
84	Ic	Me	H	CH(Et)cyclobutyl	2,4,6-Me_3-Ph
85	Ic	Me	H	CH(OEt)cyclobutyl	2,4,6-Me_3-Ph
86	Ic	Me	H	CH(Et)cyclopropyl	2,4,6-Me_3-Ph
87	Ic	Me	H	CH(OEt)cyclopropyl	2,4,6-Me_3-Ph
88	Ic	Me	H	CH$(cyclobutyl)_2$	2,4,6-Me_3-Ph

89	Ic	Me	H	CH(cyclopropyl)$_2$	2,4,6-Me$_3$-Ph
90	Ic	Me	H	NHCH(CH$_2$OMe)$_2$	2-Me-4-MeO-Ph
91	Ic	Me	H	NHCH(Et)CH$_2$OMe	2-Me-4-MeO-Ph
92	Ic	Me	H	NH-2-butyl	2-Me-4-MeO-Ph
93	Ic	Me	H	OCH(Et)CH$_2$OMe	2-Me-4-MeO-Ph
94	Ic	Me	H	O-3-pentyl	2-Me-4-MeO-Ph
95	Ic	Me	H	O-2-pentyl	2-Me-4-MeO-Ph
96	Ic	Me	H	*R*-2-pentyl	2-Me-4-MeO-Ph
97	Ic	Me	H	*S*-2-pentyl	2-Me-4-MeO-Ph
98	Ic	Me	H	*R*-2-butyl	2-Me-4-MeO-Ph
99	Ic	Me	H	*S*-2-butyl	2-Me-4-MeO-Ph
100	Ic	Me	H	3-pentyl	2-Me-4-MeO-Ph
101	Ic	Me	H	CH(Et)CH$_2$OH	2-Me-4-MeO-Ph
102	Ic	Me	H	CH(Et)CH$_2$OMe	2-Me-4-MeO-Ph
103	Ic	Me	H	COCH$_3$	2-Me-4-MeO-Ph
104	Ic	Me	H	COEt	2-Me-4-MeO-Ph
105	Ic	Me	H	CO$_2$Et	2-Me-4-MeO-Ph
106	Ic	Me	H	CO-2-pentyl	2-Me-4-MeO-Ph
107	Ic	Me	H	CO-3-pentyl	2-Me-4-MeO-Ph
108	Ic	Me	H	CH(OH)CH$_3$	2-Me-4-MeO-Ph
109	Ic	Me	H	C(OH)Me$_2$	2-Me-4-MeO-Ph
110	Ic	Me	H	C(OH)Ph-3-pyridyl	2-Me-4-MeO-Ph
111	Ic	Me	H	CH(OMe)CH$_3$	2-Me-4-MeO-Ph
112	Ic	Me	H	CH(OMe)Et	2-Me-4-MeO-Ph
113	Ic	Me	H	CH(OMe)Pr	2-Me-4-MeO-Ph
114	Ic	Me	H	CH(OEt)CH$_3$	2-Me-4-MeO-Ph
115	Ic	Me	H	CH(OPr)CH$_3$	2-Me-4-MeO-Ph
116	Ic	Me	H	CH(OMe)Et	2-Me-4-MeO-Ph
117	Ic	Me	H	CH(OMe)Pr	2-Me-4-MeO-Ph
118	Ic	Me	H	cyclobutyl	2-Me-4-MeO-Ph
119	Ic	Me	H	cyclopentyl	2-Me-4-MeO-Ph
120	Ic	Me	H	CH(Me)cyclobutyl	2-Me-4-MeO-Ph
121	Ic	Me	H	CH(OMe)cyclobutyl	2-Me-4-MeO-Ph
122	Ic	Me	H	CH(Me)cyclopropyl	2-Me-4-MeO-Ph
123	Ic	Me	H	CH(OMe)cyclopropyl	2-Me-4-MeO-Ph
124	Ic	Me	H	CH(Et)cyclobutyl	2-Me-4-MeO-Ph
125	Ic	Me	H	CH(OEt)cyclobutyl	2-Me-4-MeO-Ph
126	Ic	Me	H	CH(Et)cyclopropyl	2-Me-4-MeO-Ph

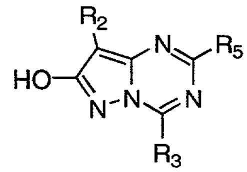
127	Ic	Me	H	CH(OEt)cyclopropyl	2-Me-4-MeO-Ph	
128	Ic	Me	H	$CH(cyclobutyl)_2$	2-Me-4-MeO-Ph	
129	Ic	Me	H	$CH(cyclopropyl)_2$	2-Me-4-MeO-Ph	
130	Ic	Me	H	$NHCH(CH_2OMe)_2$	2-Cl-4-MeO-Ph	
131	Ic	Me	H	$NHCH(Et)CH_2OMe$	2-Cl-4-MeO-Ph	
132	Ic	Me	H	NH-2-butyl	2-Cl-4-MeO-Ph	
133	Ic	Me	H	$OCH(Et)CH_2OMe$	2-Cl-4-MeO-Ph	
134	Ic	Me	H	O-3-pentyl	2-Cl-4-MeO-Ph	
135	Ic	Me	H	O-2-pentyl	2-Cl-4-MeO-Ph	
136	Ic	Me	H	*R*-2-pentyl	2-Cl-4-MeO-Ph	
137	Ic	Me	H	*S*-2-pentyl	2-Cl-4-MeO-Ph	
138	Ic	Me	H	*R*-2-butyl	2-Cl-4-MeO-Ph	
139	Ic	Me	H	*S*-2-butyl	2-Cl-4-MeO-Ph	
140	Ic	Me	H	3-pentyl	2-Cl-4-MeO-Ph	amorph
141	Ic	Me	H	$CH(Et)CH_2OH$	2-Cl-4-MeO-Ph	
142	Ic	Me	H	$CH(Et)CH_2OMe$	2-Cl-4-MeO-Ph	
143	Ic	Me	H	$COCH_3$	2-Cl-4-MeO-Ph	
144	Ic	Me	H	COEt	2-Cl-4-MeO-Ph	
145	Ic	Me	H	CO_2Et	2-Cl-4-MeO-Ph	
146	Ic	Me	H	CO-2-pentyl	2-Cl-4-MeO-Ph	
147	Ic	Me	H	CO-3-pentyl	2-Cl-4-MeO-Ph	
148	Ic	Me	H	$CH(OH)CH_3$	2-Cl-4-MeO-Ph	
149	Ic	Me	H	$C(OH)Me_2$	2-Cl-4-MeO-Ph	
150	Ic	Me	H	C(OH)Ph-3-pyridyl	2-Cl-4-MeO-Ph	
151	Ic	Me	H	$CH(OMe)CH_3$	2-Cl-4-MeO-Ph	
152	Ic	Me	H	CH(OMe)Et	2-Cl-4-MeO-Ph	
153	Ic	Me	H	CH(OMe)Pr	2-Cl-4-MeO-Ph	
154	Ic	Me	H	$CH(OEt)CH_3$	2-Cl-4-MeO-Ph	
155	Ic	Me	H	$CH(OPr)CH_3$	2-Cl-4-MeO-Ph	
156	Ic	Me	H	CH(OMe)Et	2-Cl-4-MeO-Ph	
157	Ic	Me	H	CH(OMe)Pr	2-Cl-4-MeO-Ph	
158	Ic	Me	H	cyclobutyl	2-Cl-4-MeO-Ph	
159	Ic	Me	H	cyclopentyl	2-Cl-4-MeO-Ph	
160	Ic	Me	H	CH(Me)cyclobutyl	2-Cl-4-MeO-Ph	
161	Ic	Me	H	CH(OMe)cyclobutyl	2-Cl-4-MeO-Ph	
162	Ic	Me	H	CH(Me)cyclopropyl	2-Cl-4-MeO-Ph	
163	Ic	Me	H	CH(OMe)cyclopropyl	2-Cl-4-MeO-Ph	
164	Ic	Me	H	CH(Et)cyclobutyl	2-Cl-4-MeO-Ph	

165	Ic	Me	H	CH(OEt)cyclobutyl	2-Cl-4-MeO-Ph
166	Ic	Me	H	CH(Et)cyclopropyl	2-Cl-4-MeO-Ph
167	Ic	Me	H	CH(OEt)cyclopropyl	2-Cl-4-MeO-Ph
168	Ic	Me	H	CH(cyclobutyl)$_2$	2-Cl-4-MeO-Ph
169	Ic	Me	H	CH(cyclopropyl)$_2$	2-Cl-4-MeO-Ph
170	Ic	Me	H	*R*-2-pentyl	2-Me-6-MeO-pyrid-3-yl
171	Ic	Me	H	*S*-2-pentyl	2-Me-6-MeO-pyrid-3-yl
172	Ic	Me	H	*R*-2-butyl	2-Me-6-MeO-pyrid-3-yl
173	Ic	Me	H	*S*-2-butyl	2-Me-6-MeO-pyrid-3-yl
174	Ic	Me	H	3-pentyl	2-Me-6-MeO-pyrid-3-yl
175	Ic	Me	H	CH(Et)CH$_2$OH	2-Me-6-MeO-pyrid-3-yl
176	Ic	Me	H	CH(Et)CH$_2$OMe	2-Me-6-MeO-pyrid-3-yl
177	Id	Me	H	NHCH(CH$_2$OMe)$_2$	2,4-Cl$_2$-Ph
178	Id	Me	H	NHCH(Et)CH$_2$OMe	2,4-Cl$_2$-Ph
179	Id	Me	H	NH-2-butyl	2,4-Cl$_2$-Ph
180	Id	Me	H	OCH(Et)CH$_2$OMe	2,4-Cl$_2$-Ph
181	Id	Me	H	O-3-pentyl	2,4-Cl$_2$-Ph
182	Id	Me	H	O-2-pentyl	2,4-Cl$_2$-Ph
183	Id	Me	H	*R*-2-pentyl	2,4-Cl$_2$-Ph
184	Id	Me	H	*S*-2-pentyl	2,4-Cl$_2$-Ph
185	Id	Me	H	*R*-2-butyl	2,4-Cl$_2$-Ph
186	Id	Me	H	*S*-2-butyl	2,4-Cl$_2$-Ph
187	Id	Me	H	CH(Et)CH$_2$OH	2,4-Cl$_2$-Ph
189	Id	Me	H	CH(Et)CH$_2$OMe	2,4-Cl$_2$-Ph
190	Id	Me	H	COCH$_3$	2,4-Cl$_2$-Ph
191	Id	Me	H	COEt	2,4-Cl$_2$-Ph
192	Id	Me	H	CO$_2$Et	2,4-Cl$_2$-Ph
193	Id	Me	H	CO-2-pentyl	2,4-Cl$_2$-Ph
194	Id	Me	H	CO-3-pentyl	2,4-Cl$_2$-Ph
195	Id	Me	H	CH(OH)CH$_3$	2,4-Cl$_2$-Ph

196	Id	Me	H	C(OH)Me_2	2,4-Cl_2-Ph	
197	Id	Me	H	C(OH)Ph-3-pyridyl	2,4-Cl_2-Ph	
198	Id	Me	H	CH(OMe)CH_3	2,4-Cl_2-Ph	
199	Id	Me	H	CH(OMe)Et	2,4-Cl_2-Ph	
200	Id	Me	H	CH(OMe)Pr	2,4-Cl_2-Ph	
201	Id	Me	H	CH(OEt)CH_3	2,4-Cl_2-Ph	
202	Id	Me	H	CH(OPr)CH_3	2,4-Cl_2-Ph	
203	Id	Me	H	CH(OMe)Et	2,4-Cl_2-Ph	
204	Id	Me	H	CH(OMe)Pr	2,4-Cl_2-Ph	
205	Id	Me	H	cyclobutyl	2,4-Cl_2-Ph	
206	Id	Me	H	cyclopentyl	2,4-Cl_2-Ph	
207	Id	Me	H	CH(Me)cyclobutyl	2,4-Cl_2-Ph	
208	Id	Me	H	CH(OMe)cyclobutyl	2,4-Cl_2-Ph	
209	Id	Me	H	CH(Me)cyclopropyl	2,4-Cl_2-Ph	
210	Id	Me	H	CH(OMe)cyclopropyl	2,4-Cl_2-Ph	
211	Id	Me	H	CH(Et)cyclobutyl	2,4-Cl_2-Ph	
212	Id	Me	H	CH(OEt)cyclobutyl	2,4-Cl_2-Ph	
213	Id	Me	H	CH(Et)cyclopropyl	2,4-Cl_2-Ph	
214	Id	Me	H	CH(OEt)cyclopropyl	2,4-Cl_2-Ph	
215	Id	Me	H	CH(cyclobutyl)$_2$	2,4-Cl_2-Ph	
216	Id	Me	H	CH(cyclopropyl)$_2$	2,4-Cl_2-Ph	
217	Ic	Me	H	3-pentyl	2,4-Me_2-4-MeOPh	80-82
218	Ic	Me	-	4-heptyl	2,4-Cl_2-Ph	75.5-76.5
219	Ic	Me	-	CH(Me)cyclobutyl	2,4-Cl_2-Ph	
220	Ic	Me	-	CH(CH_2OMe)Pr	2,4-Cl_2-Ph	
221	Ic	Me	-	CH(CH_2CH_2OMe)$_2$	2,4-Cl_2-Ph	
222	Ic	Me	-	CH(CH_2CH_2OMe)Et	2,4-Cl_2-Ph	
223	Ic	Me	-	CH(CH_2CH_2OMe)-cyclobutyl	2,4-Cl_2-Ph	
224	Ic	Me	-	CH(CH_2CH_2OMe) 3-tetrahydrofuranyl	2,4-Cl_2-Ph	
225	Ic	Me	-	3-pentyl	2-Cl-4-OMe-Ph	
226	Ic	Me	-	CH(Me)Pr	2-Cl-4-OMe-Ph	
227	Ic	Me	-	4-heptyl	2-Cl-4-OMe-Ph	
228	Ic	Me	-	CH(CH_2OMe)Pr	2-Cl-4-OMe-Ph	
229	Ic	Me	-	CH(Me)cyclobutyl	2-Cl-4-OMe-Ph	
230	Ic	Me	-	CH(Me)Pr	2-Cl-4,5-OMe_2-Ph	
231	Ic	Me	-	CH(Me)cyclobutyl	2-Cl-4,5-OMe_2-Ph	

232	Ic	Me	-	$CH(CH_2CH_2OMe)_2$	2-Cl-4,5-OMe_2-Ph	
233	Ic	Me	-	4-heptyl	2-Cl-4,5-OMe_2-Ph	
234	Ic	Me	-	$CH(CH_2OMe)Pr$	2-Cl-4,5-OMe_2-Ph	
235	Ic	Me	-	$CH(CH_2CH_2OMe)$ cyclobutyl	2-Cl-4,5-OMe_2-Ph	
236	Ic	Me	-	$CH(CH_2CH_2OMe)$-3-tetrahydofuranyl	2-Cl-4,5-OMe_2-Ph	
237	Ic	Me	-	CH(Me)cyclobutyl	2-Cl-4-OMe-5-FPh	
238	Ic	Me	-	CH(Me)Pr	2-Cl-4-OMe-5-F-Ph	
239	Ic	Me	-	$CH(CH_2CH_2OMe)_2$	2-Cl-4-OMe-5-F-Ph	
240	Ic	Me	-	$CH(CH_2CH_2OMe)Et$	2-Cl-4-OMe-5-F-Ph	
241	Ic	Me	-	$CH(CH_2OMe)Pr$	2-Cl-4-OMe-5-F-Ph	
242	Ic	Me	-	$CH(CH_2CH_2OMe)$-cyclobutyl	2-Cl-4-OMe-5-F-Ph	
243	Ic	Me	-	$CH(CH_2CH_2OMe)$-3-tetrahydrofuranyl	2-Cl-4-OMe-5-F-Ph	
244	Ic	Me	-	3-pentyl	2-Cl-4-OEt-Ph	
245	Ic	Me	-	CH(Me)Pr	2-Cl-4-OEt-Ph	
246	Ic	Me	-	4-heptyl	2-Cl-4-OEt-Ph	85.5-86.5
247	Ic	Me	-	CH(Me)cyclobutyl	2,4-OMe_2-Ph	
248	Ic	Me	-	3-pentyl	2,4-OMe_2-Ph	
249	Ic	Me	-	4-heptyl	2,4-OMe_2-Ph	87-88
250	Ic	Me	-	3-pentyl	2-Me-4-Cl-Ph	
251	Ic	Me	-	3-pentyl	4-OMe-Ph	
252	Ic	Me	-	3-pentyl	4-Cl-Ph	
253	Ic	Me	-	3-pentyl	2,5-Me_2-4-OMe-Ph	80-82
254	Ic	Me	-	3-pentyl	2-Cl-4-SO_2Me-Ph	
255	Ic	Me	-	3-pentyl	2-Me-4-NMe_2-Ph	
256	Ic	Me	-	3-pentyl	2-Cl-4-NMe_2-Ph	
257	Ic	Me	-	3-pentyl	2-CF_3-4-F-Ph	
258	Ic	Me	-	3-pentyl	2-OMe-4-Me-Ph	
259	Ic	Me	-	CH(Me)Pr	2-OH-4-OMe-Ph	
260	Ic	Me	-	CH(Me)Pr	2-Me-4-OMe-5-F-Ph	
261	Id	Me	-	3-pentyl	2,4-Cl_2-Ph	
262	Id	Me	-	3-pentyl	2-Cl-4,5-OMe_2-Ph	

TABLE 1a



Ex.	Formula	R^5	R^4	R^2	R^3	mp(°C)
263		Me	-	3-pentyl	2-Cl-4,5-OMe_2-Ph	249-250

In addition to examples 1-10, additional examples 11-248 and additional examples having the following R^4 (or R^5), R^2 and R^3 were or may readily be prepared according to the procedures described herein.

The preferred groups for R^5 in the compounds of formula Ic and Id are methyl (Me). For R^2, in compounds of formula Ic and Id having R^5 as Me (or C_2-C_6alkyl), the preferred groups include 3-pentyl, NEt_2, butyl, $NHCH(CH_2OMe)_2$, $NHCH(CH_2OEt)_2$,NHCH(Et)CH_2OMe, NH-3-heptyl, NH-3-pentyl, NH-2-butyl, NH-3-hexyl, NHCH(CH_2Ph)CH_2OMe, NHCH(Et)CH_2CH_2OMe, NH-cyclobutyl, NH-cyclopentyl, NEtPr, NEtBu, NMePr, NMePh, Npr_2, NPr(CH_2-c-C_3H_5), N(CH_2CH_2OMe)$_2$, morpholino, N(CH_2Ph)CH_2CH_2OMe, N(Me)CH_2CH_2OMe, N(Et)CH_2CH_2OMe, N(CH_2-c-C_3H_5)CH_2CH_2OMe, N(CH_2-c-C_3H_5)Pr, N(CH_2-c-C_3H_5)Et, OEt, OCH(Et)CH_2OMe, OCH(Et)CH_2CH_2OMe, OCH(Me)CH_2CH_2OMe, O-3-pentyl, O-2-pentyl, S-3-pentyl, S-2-pentyl, SEt, S(O)Et, SO_2Et, S-3-pentyl, S(O)-3-pentyl, SO_2-3-pentyl, S-2-pentyl, S(O)-2-pentyl, SO_2-2-pentyl, CH(CO_2Et)$_2$, C(Et)(CO_2Et)$_2$, CH(Et)CH_2OH, CH(Et)CH_2OMe, CH(Et)CH_2CH_2OMe, $CONMe_2$, $COCH_3$, COEt, COPr, CO-2-pentyl, CO-3-pentyl, CH(OH)CH_3, C(OH)Me_2, C(OH)Ph-3-pyridyl, CH(OMe)CH_3, CH(OMe)Et, CH(OMe)Pr, CH(OEt)CH_3, CH(OPr)CH_3, 2-pentyl, 2-butyl, cyclobutyl, cyclopentyl, CH(Me)cyclobutyl, CH(OMe)cyclobutyl, CH(OH)cyclobutyl, CH(Me)cyclopropyl,

CH(OMe)cyclopropyl, CH(OH)cyclopropyl, CH(Et)cyclobutyl, CH(Et)cyclopropyl, CH(OMe)cyclobutyl, CH(OMe)cyclopropyl, CH(OEt)cyclobutyl, CH(OEt)cyclopropyl, CH(Me)CH_2-cyclobutyl, CH(OMe)CH_2-cyclobutyl, CH(OH)CH_2-cyclobutyl, CH(Me)CH_2-cyclopropyl, CH(OMe)CH_2-cyclopropyl, CH(OH)CH_2-cyclopropyl, CH(Et)CH_2-cyclobutyl, CH(Et)CH_2-cyclopropyl, CH(OMe)CH_2-cyclobutyl, CH(OMe)CH_2-cyclopropyl, CH(OEt)CH_2-cyclobutyl, CH(OEt)CH_2-cyclopropyl, CH(CH_2OMe)cyclobutyl, CH(CH_2OMe)cyclopropyl, CH(CH_2OEt)cyclobutyl, CH(CH_2OEt)cyclopropyl, CH(cyclobutyl)$_2$, CH(cyclopropyl)$_2$, CH(Et)CH_2CONMe_2, CH(Et)$CH_2CH_2NMe_2$, CH(CH_2OMe)Me, CH(CH_2OMe)Et, CH(CH_2OMe)Pr, CH(CH_2OEt)Me, CH(CH_2OEt)Et, CH(CH_2OEt)Pr, CH($CH_2C\equiv CMe$)Et, CH($CH_2C\equiv CMe$)Et. The preferred groups for R^3 with R^2 and R^5 as defined above include 2,4-Cl_2-Ph, 2,4,6-Me_3-Ph, 2,4-Me_2-Ph, 2-Me-4-MeO-Ph, 2-Cl-4-MeO-Ph, 2-Cl-4,5-(MeO)$_2$-Ph, 2-Cl-4-MeO-5-F-Ph, 2-Me-4-MeO-5-F-Ph, 2,5-(Me)$_2$-4-MeO-Ph, 2-Me-4-NMe_2-Ph, 2-CF_3-4-MeO-Ph, 2-Me-4-(COMe)-Ph, 2-Me-6-Me_2N-pyrid-3-yl, 4-Me-2-Me_2N-pyrid-5-yl, 2-Me-6-MeO-pyrid-3-yl, 4-Me-2-MeO-pyrid-5-yl. Each of the compounds within the independent generic variations may readily be prepared according to the procedures described in Schemes 1-3 and 5.

For compounds of formulas Ie and If, in addition to example 10 in Table 1, the above variables for Ic and Id may be used in the compounds of formulas Ie and If except that R^5 groups are used as the R^4 variables. The following compounds may be prepared as the preferred embodiments wherein R^4 is selected from H, OCH_3, CH_3 and C_2H_5; R^2 is selected from $CH(C_2H_5)_2$, CH(c-C_3H_5)$_2$, CHC_2H_5(c-C_3H_5), $CH(C_2H_5)_2$, CH(c-C_3H_5)$_2$; and R^3 is selected from 2,4-Cl_2-Ph, 2-Cl-4-CH_3O-Ph, 2,4,6-$(CH_3)_3$-Ph, 2-Cl-4-CF_3-Ph and 2-$(CH_3)_2N$-4-CH_3-pyridin-5-yl. In addition, the methoxy group or the ethyl group in the R^1 position also preferrably includes CH_3 and H. Each of the compounds within the independent generic variations may readily be prepared according to the procedure described in Scheme 4. Compounds of formula IIa and IIb are readily prepared

according to the procedure described in Scheme 6. These compounds also preferrably have the variables shown in the examples and described above.

Utility

CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

Radioligand binding experiments

Compounds of the invention were tested for in vitro activity as CRF receptor antagonists. The tests described below demonstrated that the examples tested had K_is of 10,000 nM or less and are thus useful as CRF receptor antagonists. Preferred antagonists have or will have a K_i of 1,000 nM or less. Radioligand binding experiments were performed with membranes from rat frontal cortex to determine binding affinities (K_i's) of test compounds for the rat CRH_1 receptor using a modified version of methods described earlier (see E.B. DeSouza, J. Neurosci, 7:88, 1987). Rat cortex was homogenized in tissue buffer (containing 50 mM HEPES, 10 mM $MgCl_2$, 2 mM EGTA, and 1 μg/ml each of aprotonin, leupeptin, and pepstatin, pH 7.0 @ 23°C) using a Brinkman Polytron (PT-10, setting 6 for 10 sec). The homogenate was centrifuged at 48,000 X g for 12 min and the resulting pellet was washed by two sequential re-suspension and centrifugation steps. The final pellet was suspended to tissue buffer to a working concentration of 0.1 mg/ml protein. Protein determinations were made using the bicinchoninic acid (BCA) assay (Pierce, Rockford, IL) with bovine serum albumin as the standard.

All test compounds were prepared in assay buffer, which was identical to the tissue buffer except for the

inclusion of 0.15 mM bacitracin and 0.1% w/v ovalbumin. Binding assay were conducted in disposable polypropylene 96-well plates (Costar Corp., Cambridge, MA) and initiated by the addition of 100 μl membrane homogenate (containing 40-60 μg protein) to 200 μl of assay buffer containing radioligands (150 pM, final concentration, [^{125}I] tyr° ovine CRH; New England Nuclear, MA) and competing test compounds. Specific binding was determined in the presence of 10 μM α-helical CRH. Competition experiments were conducted using 12 concentrations of ligand (ranging from 1 X 10^{-11} to 1 X 10^{-5} M). The reactions mixtures were incubated to equilibrium for 2 hr at 23°C and terminated by rapid filtration using a cell harvester (Inotech Biosystems Inc., Lansing MI) over GFF glass-fibers (pre-soaked in 0.3 % v/v polyethyleneimine). Filters were rapidly washed 3X with 0.3 ml cold wash buffer (PBS, pH 7.0, containing 0.01% Triton X-100), dried, and counted in a gamma counter at 80% efficiency.

Binding affinities (K_i's) of ligands for the CRH_1 receptor were calculated using the iterative nonlinear regression curve-fitting programs (LIGAND) of Munson and Rodbard (Anal. Biochem. 1980, 107, 220-239) or Prism (GraphPad Prism, San Diego, CA). Data were best-fit by the one-site/state competition equation.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* **1**:572 (**1987**). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10^{-9} to 10^{-6}m) and 0.8 mg original wet weight tissue (approximately 40-60 mg

protein). Reactions are initiated by the addition of 1 mM ATP/^{32}P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 µl of [^{3}H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [^{32}P]cAMP from [^{32}P]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

The *in vivo* activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (**1990**).

Compounds may be tested in any species of rodent or small mammal.

Compounds of this invention have utility in the treatment of inbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier

selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active

ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive

displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease. The preferred indication and use for the compounds and compositions of the invention is in the treatment of depression or anxiety.